INDEX NUMBER

OCT 11 1931

Medical Lib.

Vol. II SEPTEMBER, 1931 No. 6

THE JOURNAL OF ALLERGY

EDITORIAL BOARD

H. L. ALEXANDER
EDITOR
St. Louis

WARREN T. VAUGHAN
ASSOCIATE EDITOR
Richmond

A. F. COCA
New York

A. H. W. CAULFEILD
Toronto

FRANCIS M. RACKEMANN
Boston

ALBERT H. ROWE
Oakland

PUBLISHED BI-MONTHLY

OFFICIAL ORGAN OF
THE SOCIETY FOP THE STUDY OF ASTHMA AND ALLIED CONDITIONS
THE ASSOCIATION FOR THE STUDY OF ALLERGY

PUBLISHED BY THE C. V. MOSBY COMPANY, 3523 PINE BOULEVARD,
ST. LOUIS, U. S. A.

Entered as Second Class Matter at Post Office at St. Louis, Mo.

The Journal of Allergy

CONTENTS FOR SEPTEMBER 1931

ORIGINAL ARTICLES

Investigations of the Mechanism of the Passive Transfer of Skin Sensitization. By F. E. Becker, M.D., and W. C. Black, M.D., Denver, Colo. ---- 405

Fever by Diathermy in the Treatment of Allergic Disease. By Samuel M. Feinberg, M.D., S. L. Osborne, B.P.E., and M. L. Afremow, M.D., Chicago, Ill. ---- 414

The Effects of Fever, Either Accidentally Incurred or Artificially Produced, in Bronchial Asthma. By Simon S. Leopold, M.D., and Sloan G. Stewart, M.D., Philadelphia, Pa. ---- 425

Hyperthermia Induced by High Frequency Electric Current in the Treatment of Intractable Asthma. By Hyman Miller, M.D., and George Piness, M.D., Los Angeles, Calif. ---- 436

A Study of the Reactions in Non-Sensitive Skin of Mixtures in Vitro of Reagin and Atopen. By Francis L. Foran, M.D., and Meyer R. Lichtenstein, M.D., Chicago, Ill. ---- 444

The Effect of Allergy on Allergen Absorption Following Parenteral Injections. By Milton B. Cohen, M.D., E. E. Ecker, Ph.D., and J. A. Rudolph, M.D., Cleveland, Ohio ---- 453

Economic Results From the Treatment of Pollen Asthma and Hay Fever. By Leslie N. Gay, M.D., Baltimore, Md. ---- 456

The Distribution of Reagins in the Blood Plasma. By E. L. Sherrer, M.D., Cleveland, Ohio ---- 467

The Dropping Out of Pollen Seasons (Relation of the Pollen Content of the Air to Hay Fever, Asthma, and Dermatitis of the Exposed Parts). By W. W. Duke, M.D., Kansas City, Mo. ---- 471

Studies in Urticaria: The Influence of Metabolic Factors. By Leo H. Criep, M.D., and Lawrence Wechsler, M.D., Pittsburgh, Pa. ---- 479

Basal Metabolism and Blood Calcium Studies in Asthma and Allergic Eczema. By Richard A. Kern, M.D., and Ida Teller, B.A., Philadelphia, Pa. ---- 488

Heat Sensitiveness. Report of a Case. By R. A. Wilson, M.D., Tucson, Arizona ---- 499

SOCIETY PROCEEDINGS

The Association for the Study of Allergy, Ninth Annual Meeting, Philadelphia, Pa., June 8 and 9, 1931 ---- 502

The Basal Metabolic Rate in Allergic Disease. By E. L. Alexander, Newport News, Va. ---- 507

The Female Allergic Patient. Preliminary Report. By Harry L. Huber, Chicago, Ill. ---- 508

DEPARTMENT OF REVIEWS AND ABSTRACTS

Selected Abstracts ---- 513

Index ---- 517

The Journal of Allergy

VOL. II SEPTEMBER, 1931 NO. 6

Original Articles

INVESTIGATIONS OF THE MECHANISM OF THE PASSIVE TRANSFER OF SKIN SENSITIZATION*

F. E. BECKER, M.D.

AND

W. C. BLACK, M.D.

DENVER, COLO.

THE work presented was planned with the purpose to determine, if possible, whether certain failures in passive transfer with sera from highly allergic subjects can be explained upon the basis of serum properties of the donor, blood group relationships, differences in skin susceptibility of the recipient, or some other unknown factor.

The mechanism of passive sensitization of normal human skin by the blood serum of an allergic individual, as demonstrated by Prausnitz and Küstner[1] in 1921, has been described by Coca and Grove[2] as follows: The atopic individual has in his blood a factor, called the atopic reagin, which in the presence of its specific atopen will produce the typical allergic skin reaction. This atopic reagin can be transferred in the serum to the normal human skin in which it produces a passive sensitization to the specific atopen. They state, "The atopic reagin has been demonstrable in the blood of all the individuals that we have examined who were known to be subject to hay fever or asthma and in whom the cutaneous tests resulted positively." They also state, "Not all normal skins are susceptible to local passive sensitization. About 84 per cent of normal skins are receptive, about 11 per cent are nonreceptive, and about 5 per cent are slightly receptive."

In our own work with local passive sensitization (passive transfer) we found the following two highly allergic subjects with whose sera we have been unable to sensitize the normal human skin: F. N., a flaxseed and pollen hypersensitive individual, and F. B., who is markedly hypersensitive to many pollens but no foods. As a positive control G. W. was chosen for this work. He is hypersensitive to many pollens

*From the Departments of Pathology and Clinical Pathology of the University of Colorado School of Medicine and Hospitals.

and foods, and his serum has never failed to sensitize the normal skin to the respective specific antigens.

All three individuals, F. N., F. B., and G. W., are about equally hypersensitive to pasture sage *(Artemesia frigida)*, with four-plus skin reactions and severe clinical manifestations in the presence of this pollen. Intradermal tests with pasture sage extract in the three were equally strong at the time this work was begun. Previously attempted passive transfers were made over a period of one year, thus obviating the possible objection that the conflicting results in these three individuals might result from a temporary nonallergic state. The degree of clinical manifestations in each is about the same. All three have marked seasonal hay fever and all have had seasonal asthmatic symptoms. All three have also had intensive pollen extract therapy—F. B. seasonally since 1921, G. W. since 1927, and F. N. since 1929, all obtaining about 70 per cent relief from symptoms, without change in degree of cutaneous reaction. F. N. belongs to blood group AB, F. B. to A, and G. W. to 0. A normal control, A. O. was chosen, who belongs to blood group B, and who was found to be entirely nonallergic.

METHOD OF PREPARING ANTIGEN AND SERA

Pasture sage *(Artemesia frigida)* was used as the test antigen. For this and all other antigens the method of preparation was as follows: 10 mg. of dry pasture sage pollen were incubated for two weeks at 37° C. in 10 ml. of Coca's extraction solution (Coca's solution, one part; neutral glycerin, two parts) and then diluted to 1:5,000 in Coca's solution (NaCl, 5 grams; $NaHCO_3$, 2.5 grams; liquid phenol, 4 ml.; distilled water to one liter).

The sera were obtained and prepared as follows: 10 ml. of blood from each of the four individuals were allowed to clot at room temperature. The sera were separated and diluted 1:4 with Coca's solution and filtered through Berkefeld candles. Coca's solution was used as a diluent and bacteriostatic medium. The following procedure shows that this solution is nonirritating and does not interfere with passive transfer. Serum from G. W. (sensitizing) was injected undiluted, diluted 1:4 with 0.85 per cent salt solution, and diluted 1:4 with Coca's solution. The passive transfer reactions in each instance were positive and alike in intensity. After twenty-three days at 10° C. the serum diluted with Coca's solution was sterile, nonirritating, and undiminished in activity.

PROCEDURE

Forty-eight hours after the preparation of the sera from the allergic individuals F. N., F. B., and G. W., and from the normal control A. O., 0.1 ml. of each was injected intradermally at different sites on the flexor surface of the forearm in each of a group of 23 medical stu-

dents. All injections were made at the same depth in the skin with a 27 gauge needle. Twenty-four hours later 0.05 ml. of 1:5,000 pasture sage extract was injected into each of the four sites in all members of this group except two, who were tested at forty-eight and seventy-two hours, respectively. Time of injection and appearance of the reaction were noted, and in all positive reactions the wheal and area of erythema were outlined. The results are summarized in Table I.

INTERPRETATION OF RESULTS

A positive reaction must show first, an erythema or "flare" in the surrounding skin; second, the formation of an irregularly shaped wheal; and third, some subjective sensation of itching or burning. Although there was some slight variation in intensity, these manifestations were all present in the positive reactions. At the nonreacting sites no wheal formation or itching was noted, although in a few instances slight erythema occurred. Moderate erythema may appear in an irritable skin merely as a result of trauma (Lewis[3]).

We believe that an injection of the antigen at a site previously injected with a proved normal serum is a valuable control because the test is then carried out under uniform skin conditions. A positive reaction consists of more than the simple raising of the skin by the quantity of injected fluid. A wheal must be produced with some irregularity in outline, even if well-formed pseudopodia are not seen. The itching or burning sensation is more uncertain, because subjective; however, if it is entirely absent, and the other two manifestations are not definite, the reaction should be considered at least very doubtful. The depth of the injection into the skin is also of importance. A very superficial injection may produce no reaction, and a very deep injection is difficult to interpret. An incidental inflammatory reaction in the skin following primary serum injections afforded the opportunity to study the following question:

DOES A LOCAL INFLAMMATORY REACTION INTERFERE WITH PASSIVE TRANSFER?

At the site of injection of serum from F. N. in 21 of the group members there occurred, for some unexplained reason, a considerable primary inflammatory reaction which had reached its height in twenty-four hours and had practically disappeared in forty-eight hours. There was sensible heat and an area of uniform edema and erythema, which in some instances reached a diameter of 3.5×6 cm. This serum was sterile, and produced the reaction both before and after dilution and filtration.

That this inflammatory reaction did not interfere with the skin test is shown by the fact that there was a distinct wheal formation and itching at this site in cases No. 5 and No. 14, patients who were proved

TABLE I

RESULTS OF PASSIVE TRANSFER

NO.	AGE	SEX	ALLERGIC HISTORY	ALLERGIC FAMILY HISTORY	BLOOD GROUP	TIME OF TEST	G. W. SAGE-SENSITIVE GROUP O	F. B. SAGE-SENSITIVE GROUP A	F. N. SAGE-SENSITIVE GROUP AB	A. O. NON-SENSITIVE GROUP B
1	28	M	None	Mother and Brother—Asthma	B	24 hr.	++++	0	0	0
2	27	M	None	Grandmother—Asthma	AB	72 hr.	++++	0	0	0
3	29	M	None	Brother—Hay Fever	A	24 hr.	++++	0	0	0
4	23	M	None	None	A	24 hr.	++++	0	0	0
5	30	F	None	Father—Eczema	A	24 hr.	++++	++++	++++	++++
6	37	M	None	None	B	24 hr.	+++	0	0	0
7	26	M	None	None	A	24 hr.	++++	0	0	0
8	26	M	None	Father—Hay Fever and Asthma	O	24 hr.	++++	0	0	0
9	25	M	Vasomotor rhinitis	Grandfather—Asthma	B	24 hr.	++++	0	0	0
10	24	M	None	Mother—Eczema	A	24 hr.	+++	0	0	0
11	32	M	Hay Fever (slight)	Father—Hay Fever and Asthma	AB	24 hr.	0	0	0	0
12	34	M	None	None	A	24 hr.	++++	0	0	0
13	25	M	None	None	O	24 hr.	++++	0	0	0
14	23	M	None	Sister—Hay Fever	A	24 hr.	++++	++++	++++	++++
15	23	M	None	None	B	24 hr.	++	0	0	0
16	23	M	None	Aunt—Hay Fever	O	24 hr.	++	0	0	0
17	25	M	None	None	A	24 hr.	++++	0	0	0
18	26	M	None	None	A	24 hr.	++++	0	0	0
19	27	M	None	Mother—Hay Fever and Asthma	O	24 hr.	++++	0	0	0
20	25	M	None	None	B	24 hr.	++++	0	0	0
21	27	M	None	None	B	24 hr.	+++	0	0	0
22	27	M	None	None	A	48 hr.	++++	0	0	0
23	27	M	None	None	A	24 hr.	++	0	0	0

to be naturally hypersensitive to sage. This was further controlled by a passive transfer with a mixture of the sera of G. W. (sensitizing) and F. N. (non-sensitizing). The same inflammatory reaction was noted at the end of twenty-four hours, and the site was then tested with the sage antigen. Due to the presence of the sensitizing serum from G. W. a typical positive skin reaction resulted, showing that this inflammatory reaction neither enhanced nor diminished the passive transfer.

SUMMARY OF RESULTS

In 22 of the 23 cases a typical skin sensitization was produced by the serum from G. W. (sensitizing), the reactions varying from two to four plus. No 22, tested at the end of forty-eight hours, and No. 2, at the end of seventy-two hours, showed the same results as the others. With the serum of F. B. (non-sensitizing) and F. N. (non-sensitizing) 21 out of 23 showed no reaction. With the serum from A. O., the known normal control, 21 of the 23 were also negative. No. 11 showed no reaction to all four sera, which may be explained by assuming that this individual has a so-called refractory skin. In cases No. 5 and No. 14 a strong skin reaction was produced at all four injected sites, which proves a natural hypersensitivity to sage in these individuals. The reactions were uniform, which indicates that a sensitizing serum neither enhances nor diminishes the natural reaction, and the two nonsensitizing sera likewise do not alter the natural reaction. Neither of these two individuals give any history of allergic manifestations. No. 5 has some nonseasonal nasal symptoms, which she considers are due to sinus infection. Her serum was used for passive transfer with the same technic as described, and a typical positive passive transfer with the sage antigen was obtained at the end of twenty-four hours.

In order to determine if a positive passive transfer might be obtained with other antigens to which F. N. and F. B. are hypersensitive, the injected sites of four individuals were retested at the end of seventy-two hours with marsh elder (*Iva xanthifolia*) and Russian thistle (*Salsola pestifer*), and in three cases the reactions were negative, as was expected, but in one case (No. 15) a positive test was obtained with marsh elder. A control showed that this individual is naturally hypersensitive to marsh elder. This brings the number of naturally hypersensitive individuals without clinical manifestations to three, in this group of 23, with the antigens used.

The age of this group is within the limits of twenty-three to thirty-seven years. All are males except one. In only two out of 23, a very moderate personal allergic history was obtained. On the other hand the family history is positive in 11 members of the group. Eleven are members of blood group A, six of group B, two of group AB, and

four of group O. The donors of the sera are each in a different blood group. A relationship between the blood groups of donor and recipient could not be demonstrated. The following question also has to do with blood group relationships:

CAN THE SENSITIZING FACTOR BE REMOVED FROM SERUM WITH THE ISOHEMAGGLUTININS?

Serum (sensitizing) was separated from the clot of freshly drawn blood from G. W., group O. Red blood cells in sterile 1 per cent sodium citrate in 0.85 per cent salt solution were obtained from nonallergic individuals in group A, group B, and group AB. Serum from G. W. was added, and the mixture was shaken at intervals at room temperature for two hours. At the end of this time the red cells were removed by centrifugalization. The residual serum was shown to contain no isohemagglutinins. The red cells were then washed free from serum. Intradermal injections of untreated sensitizing serum, of the serum from the serum-cell mixtures, and of the washed red cells were made in two nonallergic individuals. The results were as follows in each instance: plain serum plus four; serum minus isoagglutinins, plus four; washed red cells with absorbed isohemagglutinins, no reaction. These results were interpreted as follows, that there is no direct connection between the sensitizing factor of the serum and the isohemagglutinins, and that this factor cannot be removed with the isohemagglutinins. However, the question arose whether the sensitizing factor might be removed from the serum by contact with tissue cells.

CAN THE SENSITIZING FACTOR BE REMOVED FROM SERUM WITH FRESH TONSIL TISSUE?

Fresh tonsil tissue from a nonallergic individual, incidentally available, was ground to pulp, and mixed with a small amount of serum from G. W. (sensitizing) diluted 1:4 in Coca's solution. After standing at room temperature with frequent shaking for two hours the serum was filtered and injected intradermally in a nonallergic subject. In twenty-four hours the site was tested with pasture sage extract and a four-plus reaction was obtained. It is probable from the results of these experiments that neither red cells nor tonsil tissue absorb the sensitizing factor from the serum in vitro. Whether or not other tissues have this power in vitro has not, to our knowledge, been determined. An attempt to determine if the sensitizing factor is attached to the skin cells was also carried out in the following experiments.

IS THE SENSITIZING FACTOR PRESENT IN THE CELLS OF THE SKIN?

While the skin sensitizing factor cannot be demonstrated in the serum from F. B., it was thought that it might be present in the skin cells. To test this theory a full thickness graft was exchanged be-

tween F. B. and a nonallergic subject, T. B., who is of the same blood group. A preliminary passive transfer failed. The exchanged skin grafts from the lower quadrant of the breast, 4 cm. in diameter, were not entirely satisfactory, since considerable sloughing took place. After healing, each graft reacted to pollen extract like the surrounding skin. We hesitate to draw any conclusions from these results because of the sloughing. However, we believe that if completely successful the results would be very valuable, and that the experiment should be repeated. On account of the discomfort involved it is difficult to obtain volunteers for skin grafting. Therefore, should the conditions incidentally be opportune in a case of skin grafting, the grafts should be tested with this object in mind.

IS THE SENSITIZING FACTOR PRESENT IN THE LEUCOCYTES?

The possibility that the leucocytes might carry the sensitizing factor was investigated as follows: 25 ml. of blood from G. W. (sensitizing) were placed in 1 per cent sodium citrate in 0.85 per cent salt solution to prevent clotting, and centrifugalized strongly to separate out the leucocytes. This could be accomplished only partially. By removing the top layer of cells and again centrifugalizing, a concentrated suspension of leucocytes with a moderate admixture of red cells was obtained. This was washed in two changes of 0.85 per cent salt solution and injected in concentrated suspension intradermally in a nonallergic subject. The site tested twenty-four hours later failed to react. It seems probable from this observation that the leucocytes do not carry the sensitizing factor.

IS SOME UNKNOWN FACTOR PRESENT IN THE SERUM, WHICH CAN ACTIVATE A NON-SENSITIZING SERUM OR VICE VERSA?

Mixing equal parts of serum from a nonallergic individual with serum from G. W. and with serum from F. B. did not in any way diminish the sensitizing activity in the serum of G. W., nor did it activate the serum of F. B.; and mixing equal parts of serum from F. B. with serum from another individual, who is hypersensitive to many pollens but not to pasture sage, also failed to activate the serum from F. B., as the passively injected site failed to become sage sensitive.

CAN THE ACTION OF THE SENSITIZING FACTOR BE ENHANCED, AND IS A LOW TITER OF THIS FACTOR IN THE NONREACTING SERA RESPONSIBLE FOR THE FAILURE IN PASSIVE TRANSFER?

Since making the observations here reported, a paper by Smith and Bain[4] has appeared, in which these authors report passive transfers to a large group of children, with some failures. They conclude, in part, that sex, age, and blood group do not affect passive transfer, and that the chief factor causing variation in the production of passive

transfer is the titer of the serum. Our observations support their conclusions in part. We also find that failures in passive transfer may in some cases be due to the donor's serum rather than to some refractory condition of the recipient's skin. However, we have been unable to show that these failures are due to a low titer of the sensitizing factor in the nonreacting serum, as the two non-sensitizing sera that we investigated at no time produced passive transfer either diluted or undiluted when tested with strong or weak sage pollen extracts.

Four serial injections of 0.1 ml. of undiluted serum from F. B. (non-sensitizing) and from G. W. (sensitizing) were made at intervals of twelve hours into the same skin site, and tested twenty-four hours after the last injection with the pasture sage antigen. The same procedure was repeated with the two sera diluted 1:4 in Coca's solution. The reactions obtained in each instance with the serum from G. W. were strikingly more pronounced than those following single injections. The itching and erythema appeared almost instantaneously and the size of the wheal and that of the "flare" were about doubled. There was no appreciable difference between the serial injections of the whole serum and the diluted serum from G. W. It would appear, therefore, that serial injections enhance the reaction, and that the repetition of injections rather than the amount of the serum injected increases the sensitization. Yet the serum from F. B. either diluted or undiluted did not sensitize the skin, when serially injected. If failure in passive transfer with this serum were the result of low titer of the sensitizing factor, this procedure might reasonably be expected to produce skin sensitization.

An attempt to concentrate the sensitizing factor was made by evaporating 2.5 ml. of undiluted serum from G. W. (sensitizing) and from F. B. (non-sensitizing) in vacuo to quarter volume at room temperature. One-tenth ml. of each was then injected intradermally in a nonallergic subject, and tested in twenty-four hours with the pasture sage antigen. The reaction with the concentrated serum from G. W. was larger than the control (undiluted whole G. W. serum), but smaller and less intense than the previously described reactions following serial injections. The concentrated serum from F. B. (non-sensitizing) failed to sensitize the skin.

Smyth and Bain[5] report the fractionation of sensitizing sera, and the association of the sensitizing factor with the pseudoglobulin fraction. They believe that the antibody might be concentrated in this manner. Following their technic we separated the pseudoglobulin fraction from 2.5 ml. of serum from F. B. (non-sensitizing), which was then tested for sensitizing properties. It failed to produce passive transfer. We did not control this procedure with a known sensitizing serum. However, accepting their results, we believe that this further

demonstrates the absence of a sensitizing factor in the serum from F. B. These observations support the view that certain sera from hypersensitive individuals fail to sensitize the normal skin not because of a low titer of the sensitizing factor, but rather because of its absence from the serum.

The observations of Smyth and Bain[4] and our own suggest that the diagnostic method, using passive transfer as a means of avoiding direct testing, as introduced by Walzer and Kramer[6] and advocated by Ratner[7] should be employed only with the existence of such cases in mind.

SUMMARY AND CONCLUSIONS

1. Two out of three sera from sage hypersensitive subjects failed to sensitize the skin to the sage antigen in a group of 23 individuals.

2. The refractory sera also failed to produce positive reactions with other antigens to which the donors are hypersensitive.

3. With the positively reacting serum 22 out of 23 tests were positive, the one member of the group probably having a refractory skin.

4. Passive transfer may or may not be obtainable with the sera of patients with positive skin reactions and with marked clinical manifestations; also skin-sensitive individuals who never have had clinical manifestations may give a positive passive transfer.

5. Passive transfer is not dependent upon degree of skin sensitivity, upon clinical manifestations, upon temporary allergic state, or upon previous desensitization treatment.

6. Passive transfer is not dependent upon differences in the blood group of the donor and recipient.

7. The sensitizing factor is not absorbed in vitro by the blood cells from opposite blood groups or by fresh tonsil tissue, obtained from nonallergic individuals.

8. The leucocytes do not carry the sensitizing factor.

9. Serial injections increase skin sensitization.

10. While failure in passive transfer may be due to a refractory skin, as noted by many observers, it seems probable that it may be due in some instances to the absence of the sensitizing factor in the donor's serum.

REFERENCES

1. Prausnitz, C., and Küstner, H.: Centralbl. f. Bakt. **86**: 160, 1921.
2. Coca, A. F., and Grove, E. F.: J. Immunol. **10**: 445, 1925.
3. Lewis, Thomas: The Blood Vessels of the Human Skin and Their Responses, London, 1927, Shaw and Sons, Ltd.
4. Smyth, F. S., and Bain, K.: J. ALLERGY **2**: 181, 1931.
5. Smyth, F. S., and Bain, K.: J. ALLERGY **2**: 177, 1931.
6. Walzer, M., and Kramer, S. D.: J. Immunol. **10**: 835, 1925.
7. Ratner, Bret.: J. A. M. A. **96**: 571, 1931.

FEVER BY DIATHERMY IN THE TREATMENT OF ALLERGIC DISEASE*†

SAMUEL M. FEINBERG, M.D., S. L. OSBORNE, B.P.E., AND
M. L. AFREMOW, M.D.
CHICAGO, ILL.

WE HAVE repeatedly observed that acute infectious diseases frequently checked temporarily the symptoms of allergic disease, such as asthma or hay fever. This is especially true if the infection occurs outside of the respiratory tract. Although the literature contains surprisingly little to substantiate that observation, it is undoubtedly a common experience. Thus, Rackemann[1] says, "Asthma, hay fever, chronic vasomotor rhinitis, urticaria and infantile eczema clear up when fever occurs from any cause." Berg[2] reports two cases of chronic bronchial asthma cured following attacks of lobar pneumonia: he attributes that to the pneumococcus infection rather than to the temperature. Holst[3] says that although asthmatics may be free from attacks during an intercurrent febrile disease, relief following such infection is rare. He cites one instance in which chronic asthma disappeared after seventeen seizures of fever of unknown origin. Duke[4] is of the belief that relief from allergy following fevers occurs only in heat-sensitive individuals.

For several years we have believed that anything that would simulate acute febrile disease might produce the same result. In our search for such a method we considered the various modes of nonspecific therapy in vogue, such as ordinary vaccines, typhoid vaccine, colon bacillus vaccines, peptone, and milk injections. These probably owe their usefulness to their property of producing fever. To this end one must resort usually to intravenous injections of proteins with their accompanying danger, particularly in the allergic case. Repeated reports of serious reactions and fatalities from the injection of foreign proteins in allergic persons led us to believe that such methods would not be suitable for our purpose. We also considered the advisability of the use of hot baths for the production of fever, as used by Mehrtens and Pouppirt[5] in general paresis and other conditions. We were dissuaded, however, from using this form of treatment because the authors themselves considered it dangerous and impractical.

*From the Allergy Clinic of the Department of Medicine and the Physical Therapy Department of Northwestern University Medical School; and the Department of Medicine of Cook County Hospital.

†Read before the Ninth Annual Meeting of the Association for the Study of Allergy, at Philadelphia, June 8, 1931.

At about this time one of us (S.M.F.) learned of the experiments that were being carried on by Neymann and Osborne, which were published later[6, 7] in the use of diathermy to produce fever in the treatment of general paresis. It occurred to one of us (S.M.F.) that this form of fever therapy might be suitable in asthma and other allergies. With this object in view the present authors joined hands in order to investigate this problem.

It should be emphasized at this point that in speaking of diathermy for the production of fever, we have no reference to the usual diathermy methods used for several years in the treatment of asthma, such as that described by Gassul[8] and others. Diathermy with electrodes over the spleen or chest does not produce any appreciable rise in body temperature; as a matter of fact, in our experience such treatment does not give any relief.

A preliminary report[9] of this form of fever therapy and its results was given by us at the meeting of the Chicago Society of Allergy on April 20, 1931 (an abstract of which appeared in the JOURNAL OF ALLERGY of May, 1931).

TECHNIC

A low voltage high frequency machine was used with a maximum output of four thousand milliamperes. A low voltage high milliamperage current was employed. We used a range of current of from 3000 to 4000 milliamperes in this work. Patients vary rather widely as to the amount of current necessary to produce fever. The entire trunk is sandwiched between special metal electrodes, as described by Neymann and Osborne. The fenestration of the electrode is very essential to minimize the possibility of electrical burns. Burns are not necessary and usually result from careless technic. The electrodes are held in place by a canvas jacket. The electrodes and jacket are made by a well-known manufacturer of electrotherapeutic apparatus. The skin is anointed with a proper lubricant to insure good conductivity of current, until the body begins to perspire. Thorough insulation to prevent heat loss is necessary and to this end we used one blanket over the mattress, one rubber sheet over this, and then another blanket. The patient then is placed on the bed and one blanket followed by another rubber sheet is added. In all, the patient is covered with seven blankets. In almost all instances it was found advisable when treating severe asthmatics to have the patient propped up by a back rest. In spite of this rather difficult position for electrode application we had no burns or even the slightest discomfort. It took from one and a half to four hours for the current to produce the necessary fever. There seems to be a tendency for temperature to rise very slowly in negroes.

We found it difficult to depend upon mouth temperatures in asthmatics and so our reliance has been on rectal temperatures. The clinical thermometer was not used for recording rectal temperatures, but instead, a galvanometer of the deflection type with a thermocouple placed in the rectum. The thermocouple was calibrated before use. Another advantage besides accuracy is that the temperature can be read at any one instant without disturbing the patient.

The temperature usually rises from 0.5 to 1.0° F. after the current is discontinued. This is particularly true when the temperature rises rapidly. Maximum temperature of 103° F. to 105° F. rectally were usually employed with a sustained temperature about 101° F. for

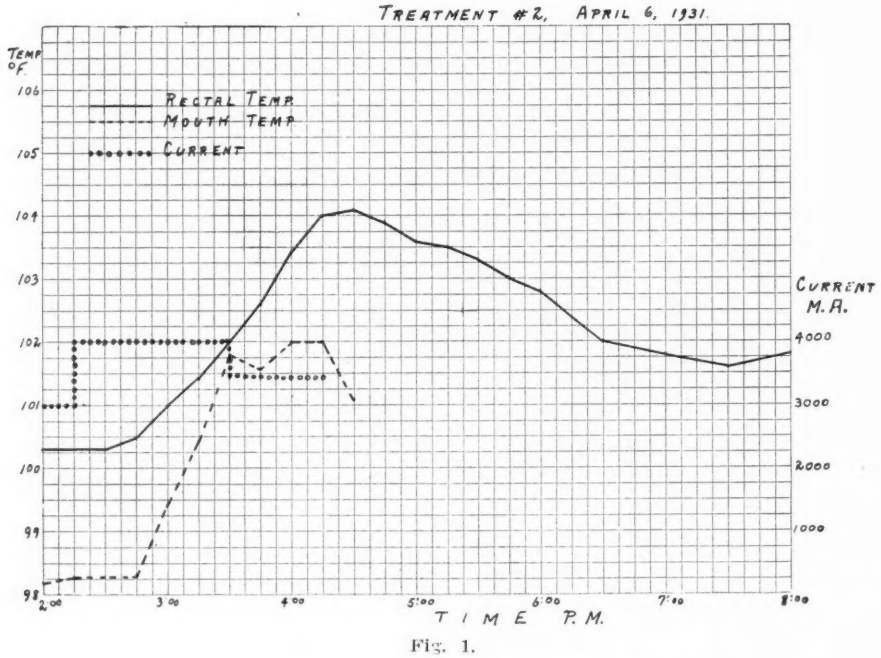


Fig. 1.

four to eight hours. It was noted that in asthma patients there is apparently a wide difference in many cases between rectal and mouth temperature. This wide difference is not apparent in general paresis or in normal persons.

The rectal and mouth temperatures usually approach each other as the treatment progresses. It appears that when the two temperature curves approach each other very closely or cross one another there is a tendency for the appearance of unfavorable reactions.

We have, in the majority of instances, arbitrarily given two treatments with an interval of two or three days, between treatments. In three or four cases we have repeated the treatment after an interval of several weeks. In one case a series of treatments of two a week

were given. We are not prepared at this time to state definitely what constitutes a proper course of treatment. We are quite certain, however, that there will have to be a variation of such technic to suit the individual requirements.

MANAGEMENT OF PATIENT

For each treatment it is necessary to hospitalize the patient for twenty-four hours. The meal preceding the treatment should be very light and consist principally of fluids. A full meal tends to make the patient quite uncomfortable. During the fever, fluids should be given freely. This may consist of plain cold water or may take the form of lemonade or orangeade. The free use of fluids has apparently very little effect on the temperature, while the withholding of it may make the patient extremely uncomfortable and ill. If an attack of asthma supervenes, adrenalin may be used. When the required fever period is drawing to a close and the patient's temperature has not dropped to 100° F., several blankets are removed in order to cool him more rapidly. It may be necessary at this point to remove all blankets and even the jacket and electrodes. It is important at this time to take care that no drafts are present. When the temperature has reached 100° F., a sponge bath is given and the bed is freshly prepared. A full diet is in order from then on, unless special conditions contraindicate it. The next morning the patient may be out of bed and may leave the hospital if necessary.

REACTIONS TO TREATMENT

In general the reactions to this form of diathermy treatment are the same as those associated with fevers of infectious origin. However, due to the fact that the temperature rises more rapidly than in infections, thus giving the physiologic mechanisms less time for adjustment, the reactions may be more marked. At about 102° F. the patient is quite restless: this restlessness often becomes lessened when higher temperatures are reached. At the height of the fever the pulse rate may range from 100 to 160, but is most frequently around 130. The blood pressure shows a tendency for increased pulse pressure, due mainly to definite decrease of diastolic pressure. Usually there is profuse perspiration, especially during the first part of the treatment. It has been noted that when the perspiration ceases or diminishes markedly, the patient is very uncomfortable and restless. The respiratory rate is moderately increased. During the height of the fever the patient usually complains of weakness. Nausea is present at times. Occasionally there are other nervous phenomena, such as numbness of the extremities or muscle spasms.

It is possible that reactions from this form of treatment might be more severe if we were to encounter a heat-sensitive individual.

TABLE I

PATIENT	DURATION AND TYPE OF ASTHMA	PREVIOUS LABORATORY TESTS	SKIN TESTS	PREVIOUS TREATMENT	DIATHERMY TREATMENTS	RESULTS
B. M. ♂—age 38	2 yr. Chronic. Attacks nightly, 5 P.M. to bedtime	Eosinophilia 4%	Negative	Medicinal	Mar. 6 and 9, 1931	4 light attacks of asthma during following 3 months
S. G. ♂—age 46	10 yr. Severe, chronic, constant. Emphysema. Uses considerable ephedrin	X-ray—emphysema, peribronchitis. EKG.—slurring QRS	Negative	House dust, vaccines, tuberculin, parathormone, NaI, HCl, tonsillectomy, ultraviolet ray, x-ray, diathermy to spleen	Feb. 10 and 12; Mar. 23, 1931	2 attacks first 12 days, light form. Next 29 days mild asthma, no medication. Then 1 fever treatment. Next 3 weeks mild asthma, then more severe
J. P. ♂—age 43	11 yr. Constant cough and asthma. Ephedrin 3 times daily. Asthma powders frequently. Marked emphysema. Canary breeder	Eosinophilia 3-20%	Canary bird feathers. Feathers, egg, chicken, house dust	Injections of egg, goose feathers, canary bird feathers, house dust, vaccines, NaI. 76 ultraviolet treatments. In clinic 7 yr.—no relief	Mar. 2 and 4; Apr. 13 and 15, 1931	No asthma first 5 days. Next 4 weeks only slight wheezing at times. Then recurrence. Following second course he had 2 days' freedom, then moderate asthma
J. W. ♂—age 43	13 yr. Asthma constant. Emphysema. Alcohol addict. Baker	EKG.—left axis deviation	Wheat Egg Vegetables	Wheat elimination and desensitization. Diets. Vaccines. No relief	Feb. 23 and 25, 1931	Free 12 days. Then practically the same as previously
P. F. ♂—age 40	34 yr. Chronic and daily for many years. Coughs daily. Severe chronic case. Emphysema. Teamster	X-ray—peribronchitis	Horse dander Feathers House dust	Injections horse dander, house dust, vaccines. No benefit	Mar. 18 and 20, 1931	Improvement began on Mar. 3. Following 8 days no asthma, but dyspnea on exertion. No report since then
H. R. ♀—age 22	Asthma and eczema since 5 weeks old. Adrenalin-fast. Asthma extreme type		Egg, pork, milk, wheat, silk	Diets. Desensitization	Feb. 27, 1931	No relief
E. M. ♀—age 45	15 yr. Chronic bronchitis followed by 1 yr. severe asthma. Several attacks daily	Secondary anemia	Negative	Vaccines	Mar. 25 and 27, 1931	No asthma from Mar. 29 to Apr. 14. No report since Apr. 14
H. S. ♂—age 41	2½ yr. Severe, chronic asthma. Several attacks daily. Emphysema	Emphysema	Negative	Nasal polyps removed	Feb. 18, 1931	No report

TABLE I—CONT'D

PATIENT	DURATION AND TYPE OF ASTHMA	PREVIOUS LABORATORY TESTS	SKIN TESTS	PREVIOUS TREATMENT	DIATHERMY TREATMENTS	RESULTS
F. T. ♂—age 43	2½ yr. Very severe, intractable asthma. Constant dyspnea. Several injections adrenalin daily. Marked emphysema. Emaciation	Emphysema	Negative	House dust, tuberculin, ultraviolet	Mar. 31 and Apr. 2, 1931	Next 2 months marked improvement. Only 1 injection adrenalin daily. Gained 12 lb.
M. Q. ♂—age 45	Severe, chronic and constant asthma. Considerable bronchitis		Negative	Various	Apr. 6 and 8, 1931	For 1 mo. after Apr. 8 he had one mild attack each night, relieved by ⅜ gr. ephedrin. Now severe asthma has returned
C. S. ♂—age 22	Asthma constant 1½ yr. Lately very severe		Negative	Medicinal. Tonsillectomy	Mar. 6; Apr. 3, 17, 24, 27, and 30; May 22, 1931	Asthma ceased Apr. 9. Asthma-free for 1 mo. Then one attack. Now has slight wheezing but no dyspnea. Feels well
J. H. ♂—age 60	3 yr. Chronic, severe. Practically never free. Adrenalin 7 or 8 times daily. Dyspnea between attacks. Aortitis, emphysema	X-ray—aortitis, peribronchitis. Wassermann ++++	Negative	Vaccines, antiluetic	Apr. 20 and 22; May 11 and 13, 1931	Adrenalin reduced to 2-4 times daily after first course. After second course improvement more marked. Only a little adrenalin at night. Now doing physical work, the first in 3 yr.
H. C. ♂—age 40	6 yr.—followed hay fever. Chronic, fairly severe. Wheezing daily but not extremely uncomfortable. Baker	Eosinophilia 4%	Wheat, fish, vegetables, ragweeds, grasses	Wheat desensitization. Vaccines	May 6 and 8, 1931	No asthma since May 7 (4 weeks)
A. N. ♂—age 59	11 yr. Chronic, severe. Practically never free. In clinic 7 yr. Emphysema	X-ray—peribronchitis. EKG.—slurred QRS and flattened T in I & II	Negative	Vaccines, tuberculin, ultraviolet ray, 3 x-ray courses	May 22 and 25, 1931	June 2 reports much improved. Slight asthma, but no adrenalin

TABLE I—CONT'D

PATIENT	DURATION AND TYPE OF ASTHMA	PREVIOUS LABORATORY TESTS	SKIN TESTS	PREVIOUS TREATMENT	DIATHERMY TREATMENTS	RESULTS
A. M. ♀—age 39	6 yr.—followed influenza. Chronic. Uses considerable ephedrin	Eosinophilia 6%. EKG.—slurred R in II & III. Flattened T in II and sharply inverted in III. Possible coronary disease	Negative	Vaccines, house dust, x-ray therapy	May 15 and 18, 1931	Slight improvement first few days. No report since then.
M. C. ♀—age 38	8 yr. Severe, chronic. Adrenalin 6-12 times daily. Emphysema. chronic bronchitis		Negative	Vaccines, house dust ultraviolet ray, x-ray, tuberculin, sulphur injections	May 27; June 1, 1931	June 5 reports only slight improvement
P. L. T. ♀—age 45	? yr. Severe		Negative	Vaccines	May 29; and June 2, 1931	No report

THERAPEUTIC RESULTS

When this work was planned, we were well aware of the limitations we would meet with in this treatment, especially in the presence of complications. We expected that this treatment might do all that an acute infection or nonspecific therapy could accomplish. We had no false hopes of obtaining cures or possibly even of obtaining relief in asthmatic patients complicated by emphysema or chronic bronchitis. However, we felt that in order to obtain a preliminary evaluation of this treatment without any undue loss of time and without treating a very large number of patients, it would be advisable to treat only those patients who had a chronic and severe asthma. We therefore selected a group of asthmatic patients, most of whom had been attending our asthma clinic for a long period; in one instance as long as seven years, without any definite improvement. It may readily be seen that this group consisted of cases far worse than the average, most of them having irremediable complications. We felt that benefit to such a class of asthmatic patients would give us encouragement in the method.

We have thus far treated 17 asthmatic patients. Of this number one had one treatment (one-half course) and we have not heard from him, and another had one treatment without benefit. Four patients have been treated very recently so that the results cannot be ascertained as yet, although they seem encouraging. Four patients with only slight complications were totally relieved: one has been relieved for three months and is still asthma-free; one had a slight recurrence after one month's freedom; a third has been relieved for over seven weeks without recurrence, and the fourth has been recently relieved. The remaining patients have had some measure of relief, either in the severity of the asthma or in the number of attacks.

The improvement most frequently begins on the second or third day after treatment, but in many instances the effect was noticeable the same day. Frequently, the patient began the treatment with wheezing, which disappeared as the treatment progressed.

Perhaps these results are not what one might desire, but when we consider the fact that these results were obtained on patients who were unable to obtain relief by any other procedure, the accomplishments seem gratifying.

Many of these patients were improved in general health, as evidenced by increased energy, increased appetite, and gain in weight.

Table I gives a brief résumé of these cases.

LABORATORY DATA

It is not our intention at this time to make a complete report of laboratory data—these will be amplified in a future presentation. However, we wish to call attention to some tendencies we have noted.

The erythrocyte count shows usually a moderate (about 10 per cent) increase during the fever. This is undoubtedly a blood-concentration effect. The leucocyte count in most cases was definitely increased, in some instances as much as 100 per cent. In most cases the preexisting eosinophilia was markedly reduced during the fever, but returned the following day.

There appears to be a slight tendency toward acidosis during the treatment, as evidenced by the CO_2 combining power of the blood plasma. We are reserving a detailed report of this work until we have accumulated more data. Recently it has been claimed[10] that allergy is a state of potential alkalosis. In support of that theory the exponent cites a number of conditions accompanied by acidosis, among which is infectious fever, that have a beneficial effect on allergic manifestations. In order to test this hypothesis we proceeded to alkalinize a group of patients. We found that in spite of alkalinization improvement still occurred.

Five patients had definitely positive skin tests. In this group intradermal tests with dilutions of the allergens showed no appreciable change after treatment. Quantitative determination of the atopic reagins in these patients before, during, and after treatment showed no decided variation.

It may be well to cite briefly one or two typical case reports:

CASE 1.—S. G., white male, aged forty-six years, fairly well-nourished, has had asthma for ten and a half years. The last few years it has become chronic. His dyspnea is constant with frequent spasmodic attacks. He uses a great deal of ephedrin. He has a marked emphysema and the roentgenogram shows emphysema and peribronchitis. The electrocardiogram reveals a slurring of the QRS complex. His skin tests are negative except for slight reactions to feathers and to house dust. He has been attending the allergy clinic of the Northwestern University Medical School for three and a half years. During this time he has had treatment with house dust, old tuberculin, autogenous vaccines, stock vaccines, parathormone, hydrochloric acid, sodium iodide intravenously, numerous quartz light treatments, x-ray treatments, and 33 diathermy treatments with electrodes placed over the splenic area. None of these measures has given him relief. During this period he had a tonsillectomy, followed by three weeks' freedom from asthma, probably due to the nonspecific effect of the necrotic tissue in the throat.

Diathermy fever treatment was given on February 10 and 12, 1931. During the next twelve days he had two days of asthma, both attacks in light form, not necessitating the use of medication. For the next twenty-nine days he had light asthma, but was much more comfortable than before the treatment. On March 23 he had another fever treatment. For the next three weeks his asthma consisted of two or three hours of wheezing during the evening which was relieved by ⅜ grain of ephedrin. Now, after two months of improvement, the asthma has become more severe.

CASE 2.—B. M., colored male, aged thirty-eight years, developed asthma two years ago following a cough of short duration. He has asthma every evening from about five o'clock until bedtime. Occasionally he has an attack on arising in the

morning. Physical examination is essentially negative. The sputum is typically asthmatic; the urine and roentgenogram are negative. There is a four per cent eosinophilia. All skin tests are negative. On March 6 and 9, 1931, he was given fever treatment. Following that he went seventeen days without an attack. Then he had two attacks of usual asthma followed by nine days of freedom. Two days of asthma again occurred. At the present writing (June 3, 1931) there has been no return of the asthma.

DISCUSSION

There is no doubt that fever treatment by diathermy as here described is capable of giving benefit to some sufferers from asthma. Disadvantages to this form of treatment are its expense due to overnight hospitalization, discomfort to the patient, the time-consuming element to the operator, the comparatively temporary nature of the relief, and the incomplete knowledge of the limitations of its uses. We are attempting to overcome some of these difficulties by experimenting with variations in technic and other observations. It must be emphasized at this point that it is necessary to use caution in the selection of cases for this treatment. The treatment is strenuous and apparently places a temporary burden on the heart. It is necessary to make careful preliminary studies on the patient before such treatment is undertaken. Furthermore, we have thought it best, at least for the present, to limit this treatment to those persons who have resisted all ordinary forms of treatment. We are also investigating the use of this form of therapy in other allergies, such as hay fever, hyperesthetic rhinitis, and urticaria.

At this time we have no intention of entering into a discussion of the mechanisms involved in the production of relief by this fever therapy. However, our experiments thus far lead us to believe that it lies neither in a change in the acid-base balance of the blood nor in the sensitiveness of the patient to the allergen, at least as far as skin-sensitivity is concerned. Neither does it depend on any decided changes in the reagins. Developments in future experiments may possibly furnish us with a clue for this interesting phenomenon.

SUMMARY

Fever by diathermy is presented as a method of nonspecific treatment of allergic disease. A number of severe asthmatic patients treated by this method gave results which are regarded as highly encouraging. The fact is stressed that a careful study of the individual case will have to be made before such treatment may be considered either necessary, advisable, or safe.

We wish to express our thanks to Dr. John S. Coulter, director of the department of physical therapy of the Northwestern University Medical School, for his valuable suggestions, interest, and aid in this work.

REFERENCES

1. Rackemann, F. M.: Clinical Allergy, New York, 1931, p. 484, The Macmillan Co.
2. Berg, S.: Relief of Bronchial Asthma Following Lobar Pneumonia, J. ALLERGY **2:** 54, 1930.
3. Holst, P. F.: Norsk. Mag. f. Laegevidensk. **83:** 577, 1922.
4. Duke, Wm. W.: Heat and Effort Sensitiveness, Cold Sensitiveness, Arch. Int. Med. **45:** 206, 1930.
5. Mehrtens, H. G., and Pouppirt, P. S.: Hyperpyrexia Produced by Baths, Arch. Neurol. & Psychiat. **22:** 700, 1929.
6. Neymann, C. A., and Osborne, S. L.: Artificial Fever Produced by High Frequency Currents. Preliminary Report, Illinois M. J. **56:** 199, 1929.
7. Neymann, C. A., and Osborne, S. L.: The Treatment of Dementia Paralytica With Hyperpyrexia Produced by Diathermy, J. A. M. A. **96:** 7, 1931.
8. Gassul, R.: Desensibilisierungsversuche beim Asthma bronchiale mittels Milzdiathermie, Deutsche med. Wchnschr. **52:** 1735, 1926.
9. Feinberg, S. M., Osborne, S. L., and Afremow, M. L.: A New Method of Nonspecific Treatment of Allergic Disease. Preliminary Report. (Abstract of paper read before Chicago Society of Allergy, April 20, 1931), J. ALLERGY **2:** 291, 1931.
10. Beckman, Harry: Allergy and the Acid-Base Balance, J. A. M. A. **95:** 1582, 1930.

185 N. WABASH AVENUE.

(For discussion, see page 503.)

THE EFFECTS OF FEVER, EITHER ACCIDENTALLY INCURRED OR ARTIFICIALLY PRODUCED, IN BRONCHIAL ASTHMA*†

SIMON S. LEOPOLD, M.D., AND SLOAN G. STEWART, M.D.
PHILADELPHIA, PA.

CLINICAL experience has taught us that in chronic bronchial asthma intercurrent infections of various types, sufficiently severe to produce pronounced febrile reaction, frequently are attended by freedom from asthmatic paroxysms for their duration and for a variable period thereafter.

That various other chronic diseases may be favorably influenced by intercurrent infections, accidently or deliberately acquired, is a clinically established fact.

Verily, there is nothing new under the sun! One hundred and thirteen years ago, Dr. Nathaniel Chapman,[1] in a lecture to the students of the University of Pennsylvania, on the practice of physic, in speaking of malarial fevers, stated: "The intermittents do sometimes cure other diseases as gout, rheumatism, acute and chronic; chronic cutaneous eruptions are also frequently cured by them; spasmodic complaints as chorea, epilepsy, *asthma*, hysteria, mania and especially melancholia. I have told you it is the fashion in Europe to send patients with pulmonic complaints to miasmatic countries and you have heard of the practice being used in our own country."

In 1850, Morris[2] reported in the *New Orleans Medical and Surgical Journal* a patient who was cured of hemiplegia by accidentally becoming infected with malaria.

The Wagner-Jauregg[3] malarial treatment of paresis introduced in 1917 is an accepted therapeutic procedure of established value.

Because of the dangers of deliberately introducing a new disease, even for therapeutic purposes, into the human body already otherwise afflicted, numerous other measures have been employed to produce therapeutic fever.

Various forms of foreign protein therapy, particularly by intravenous injection, have been most extensively used. For reasons which are obvious, this method is particularly hazardous in the treatment of an allergic individual; and, generally speaking, response to it is too violent and too brief. Therefore, attention was directed toward some mechanical means which would serve this purpose. Those which

*From the Allergy section of the medical division of the hospital of the University of Pennsylvania.

†Read at the Ninth Annual Meeting of the Association for the Study of Allergy at Philadelphia, June 8, 1931.

have been used have been continuous hot baths, employed by Schamberg and Tseng[4] in the treatment of syphilis, continuous exposure to heated air and various forms of electrical apparatus.

The first machine for this purpose was devised by Dr. Whitney,[5] Director of the Research Laboratories of the General Electric Company, as the result of his observation that men working in the field of a short wave radio transmitter experienced an elevation of body temperature. The General Electric machine is constructed on the principle of a short wave radio transmitter, the energy being concentrated between two condenser plates, instead of being directed from an aerial. While this machine is extremely efficient in rapidly raising body temperature, it is prohibitively expensive, dangerous even in expert hands, because of the likelihood of producing burns, and, therefore, not yet commercially available.

More recently, King and Cocke[6] used a high-frequency diathermy machine by means of which, by the use of proper electrodes and by thorough insulation of the patient, they were able to raise body temperature. A similar high frequency apparatus which delivers 3,000 milliamperes at a high frequency of 1,750 kilocycles has been employed in our study.

Within the past week our attention has been directed to a preliminary report by Feinberg, Osborne and Afremow[7] presented at the April meeting of the Chicago Society of Allergy, and published in abstract in the current number of the JOURNAL OF ALLERGY. These authors have worked on the same problem, utilizing a similar diathermy machine.

The following five case reports with their accompanying charts represent the effects of various intercurrent infections on the course of chronic bronchial asthma. The sixth chart shows a typical febrile reaction, artificially induced by diathermy, and the seventh, the febrile response of a single patient, to each of ten treatments over a period of 16 days, together with the daily number of asthmatic attacks during this period.

CASE REPORTS

CASE 1.—J. B., a man, aged 38, was first admitted to the University Hospital on November 26, 1929. His symptoms began in September, 1926, with paroxysms of sneezing, probably the result of his first attack of Fall hay fever. In October, 1926, he became severely asthmatic, probably due to pollen asthma. Since that time, the asthmatic seizures were practically continuous. In the subsequent three years, nine nasal operations were performed, either with periods of short temporary relief or none. He lived in Arizona for a year but remained unimproved. During his first admission to the Hospital, three further operations for pan-sinusitis were undertaken without appreciable effect. He

was readmitted on November 11, 1930, and subjected to further nasal surgery, including cocainization of the sphenopalatine ganglion.

Four days after surgical drainage of the left sphenoid sinus on March 1, 1931, the patient developed an extensive facial erysipelas.

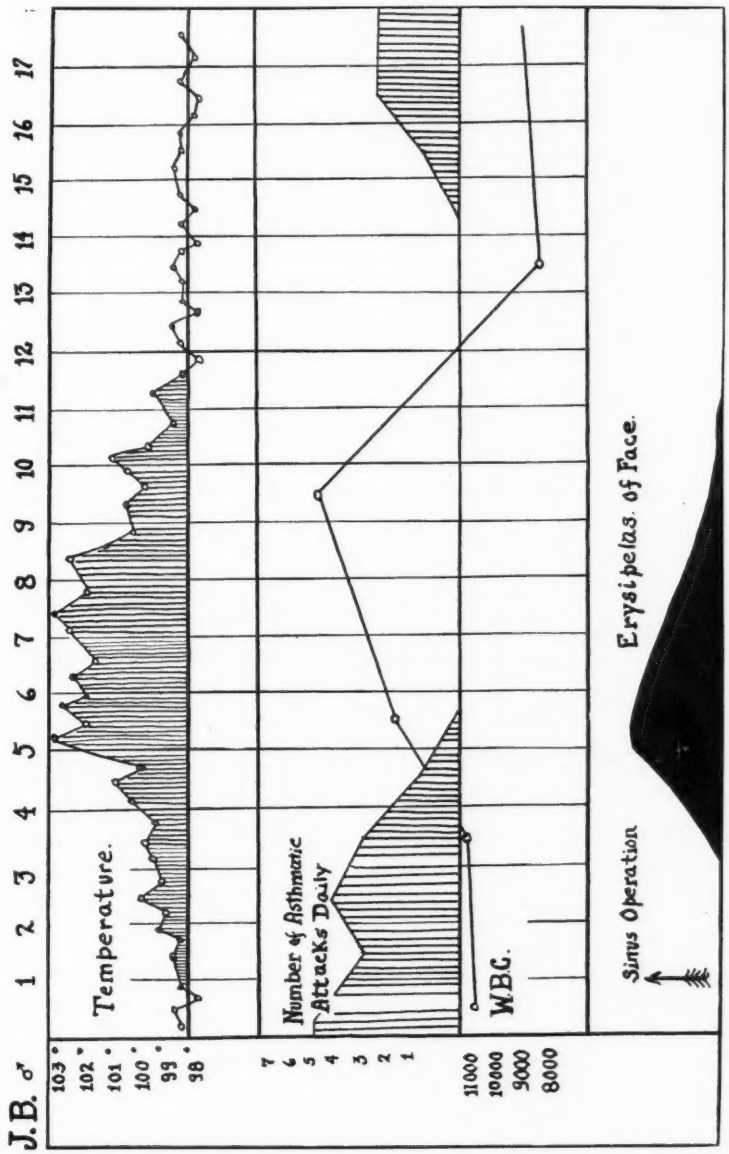


Fig. 1.—Case 1. Illustrating the complete cessation of asthmatic attacks during the course of an accidentally acquired attack of facial erysipelas. Note the marked febrile reaction and the leucocytosis which reached 25,000 on the fifth day of the disease.

The asthmatic attacks stopped abruptly and completely during this time and for a few days thereafter.

CASE 2.—A. M., a woman, aged 36, developed her first attack of asthma in March, 1930. The attacks have continued without remission and were apparently aggravated by a sinus operation in December, 1930.

At the time of her first admission to the University Hospital, she was severely asthmatic, and at this time there was clinical and roentgenologic evidence of bronchopneumonia, despite the absence of a febrile reaction. The number of asthmatic attacks averaged six in 24 hours.

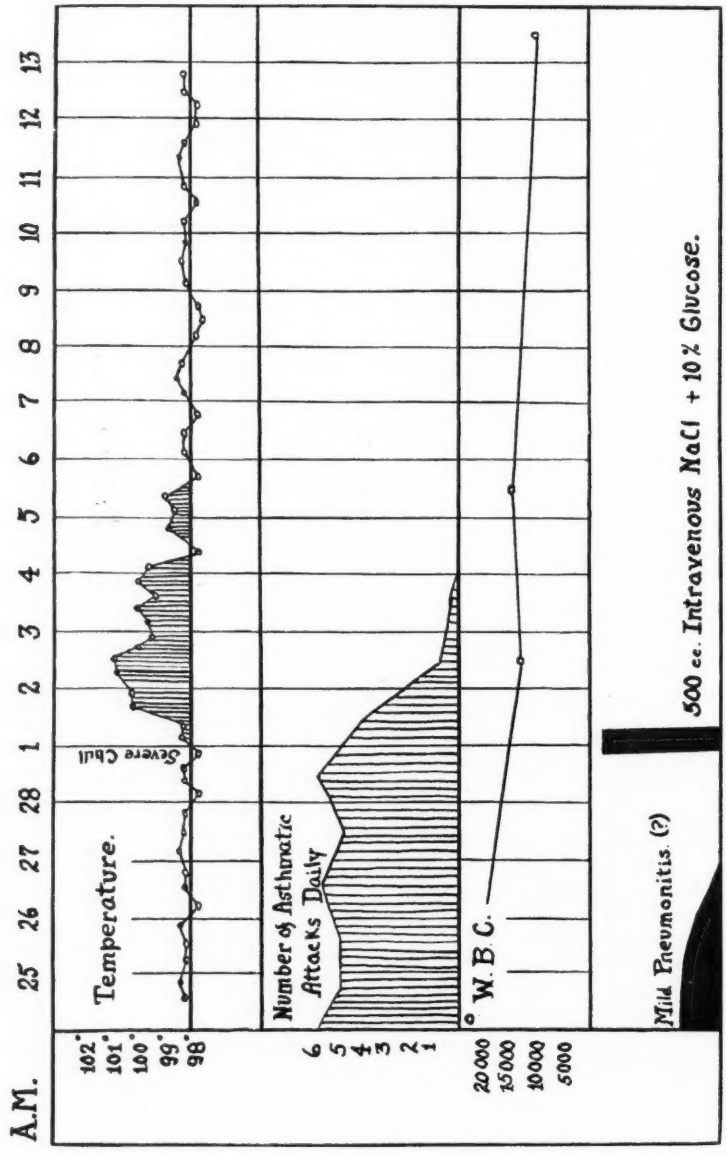


Fig. 2.—Case 2. Illustrating the complete though temporary cessation of asthmatic attacks in a chronic asthmatic patient, following the febrile reaction accidentally produced by an intravenous injection of saline and glucose. In this case, there was an initial leucocytosis probably due to an intercurrent attack of bronchopneumonia without febrile reaction. The intravenous injection had no effect on the leucocyte counts.
This chart does not show the complete cessation of asthmatic attacks which followed a recent attack of bronchopneumonia with marked febrile reaction.

On March 1, 1931, because of vomiting and dehydration, the patient was given 500 c.c. of normal salt solution with 10 per cent glucose, intravenously. Despite the fact that this was given over a period of 40 minutes there was a severe chill, with a febrile reaction which lasted

four days. The asthmatic attacks stopped abruptly and completely, following this reaction, and except for a single seizure on March 19 did not recur until April 3.

This patient was readmitted to the Hospital with severe asthma on May 6, 1931, and on May 12 developed an attack of bronchopneumonia,

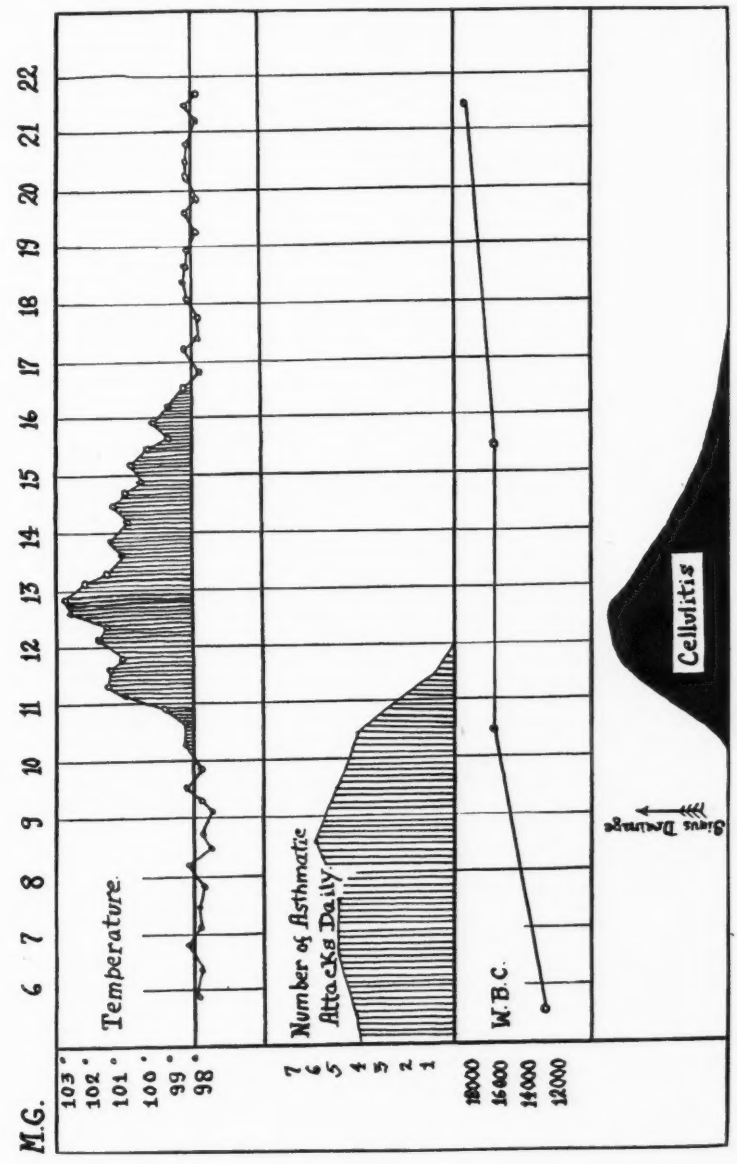


Fig. 3.—Case 3. This chart represents the occurrence of asthmatic attacks in relation to the febrile reaction which accompanied the severe attack of cellulitis of the face. There was a persistent leucocytosis.

this time accompanied by a temperature reaching 104° F. During this attack and since, she has been entirely free of asthma.

CASE 3.—M. G., a woman, aged 56, first experienced mild asthmatic seizures shortly after a severe cold in 1923. After sinus operation and

tonsillectomy in 1924 the asthma improved for seven months. Further nasal surgery was required in 1925 and 1929 because of the severity and frequency of asthmatic attacks. There were as many as eight or ten attacks during 24 hours. Asthma was practically continuous be-

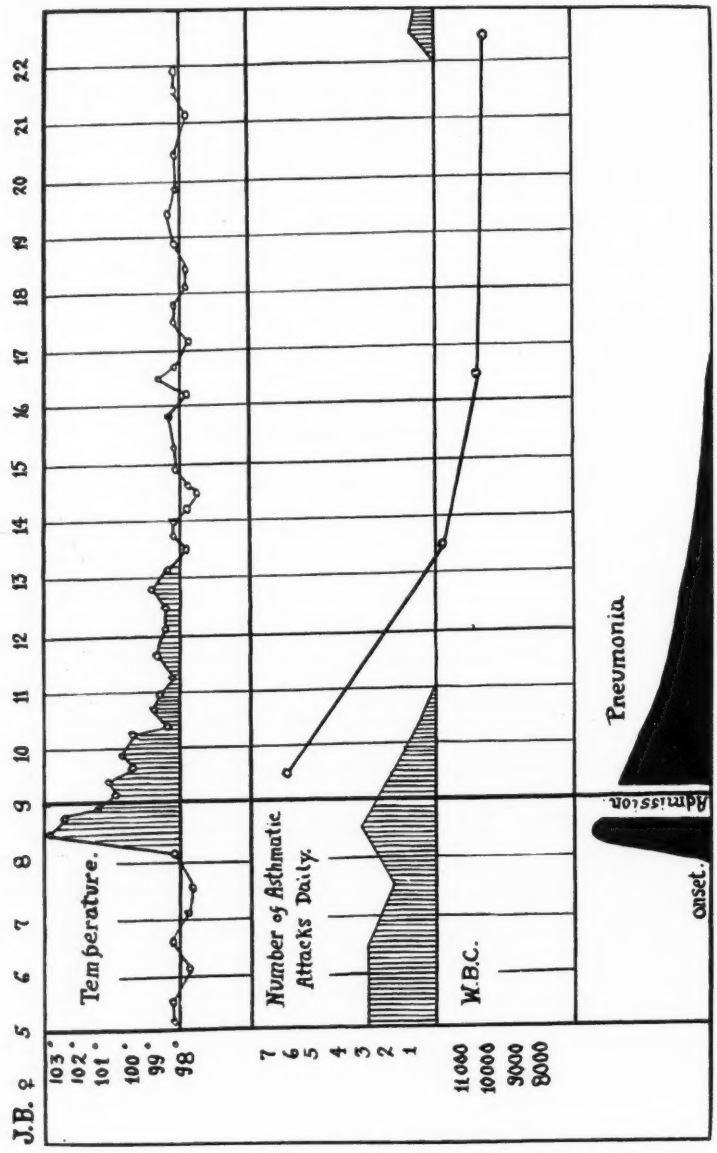


Fig. 4.—Case 4. In this case the fever and leucocytosis were of short duration but the relief of the asthmatic attacks was complete for approximately the same period of time as in the first and third cases.

fore admission. There was no other personal history or family history of allergy. Sinus roentgen-ray examination revealed clouding of all of the sinuses.

Three days after a bilateral maxillary drainage and sphenoid exenteration, the patient developed a rather severe case of erysipelas of

the face which lasted eight days. Several days after the onset of this acute streptococcus infection, the asthmatic attacks completely stopped and the patient was free of asthma for two weeks. The attacks gradu-

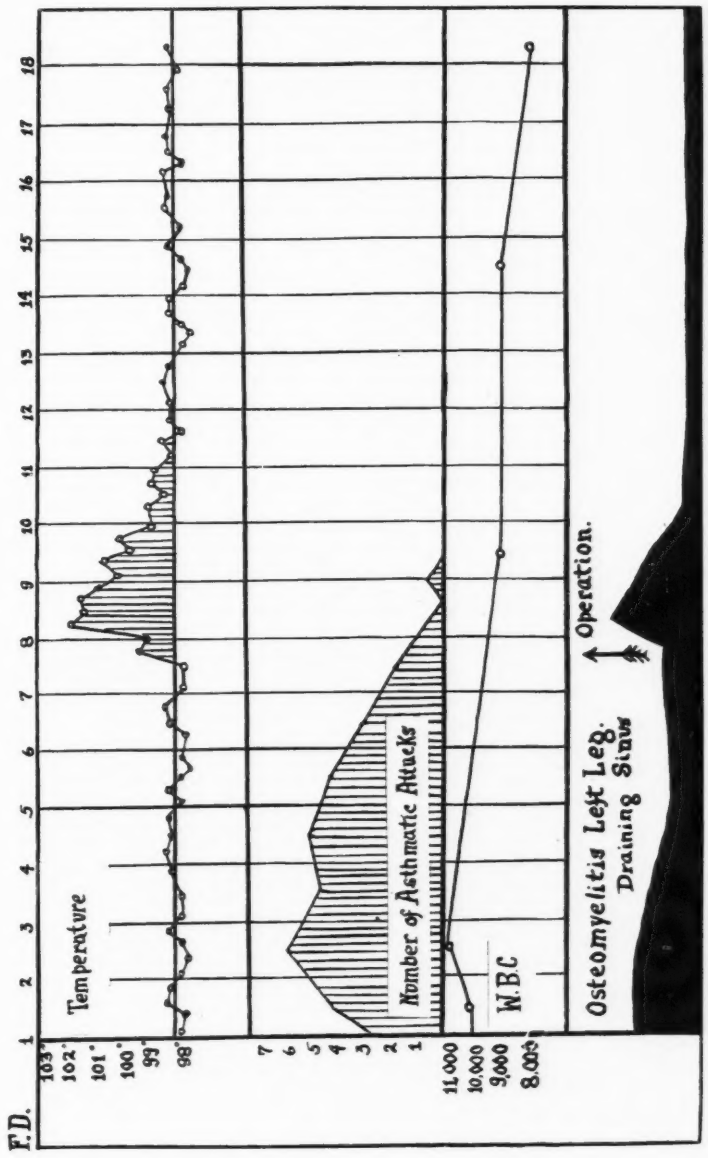


Fig. 5.—Case 5. Chronic infection, in the form of osteomyelitis of the left femur was not completely eradicated by operation. The febrile response was quite mild and no leucocytosis was noted at the time of the cessation of the asthma.

ally began to return and had soon become as severe as they had been before the infection developed.

CASE 4.—J. B., a woman, aged 52, came into the hospital with bronchopneumonia. For 12 years the patient has had hay fever and for eight years bronchial asthma. During the past few years asthmatic attacks

have become more severe and the number of attacks have averaged two or three a day. There is no history of collateral allergy.

Three days after the onset of pneumonia the asthma stopped abruptly for 12 days. It then recurred with its usual frequency of attacks.

CASE 5.—F. D., a man, aged 56, had had an area of chronic osteomyelitis in the left femur for 40 years, following a gunshot wound of the leg. A small amount of drainage was noted at times from a sinus in the left thigh.

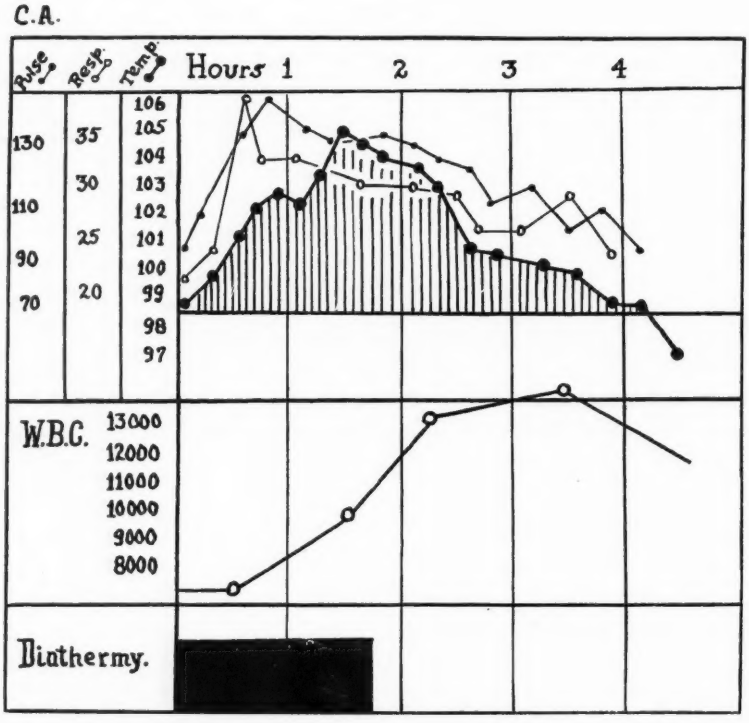


Fig. 6.—This chart depicts the patient's response to diathermy. This was administered for a little less than two hours. As the temperature rose, the patient experienced great discomfort, especially nausea, weakness and restlessness. At a temperature of 104° the patient became delirious and by the time it had reached 105° it seemed dangerous to continue. There were cyanosis and tachypnoea. The pulse rate had reached 150 beats per minute. Fever persisted, gradually falling to normal two hours after diathermy had been discontinued. The degree of leucocytosis produced by the febrile reaction in one treatment, as charted, is more marked than the response found in the majority of other treatments.

For 14 months there had been severe paroxysms of asthma which became ever more severe. The first attack followed a cold, possibly influenza. When the patient was admitted to the hospital, the asthmatic attacks occurred from five to seven times in 24 hours. There was no family or personal history of allergy. Sinus x-rays revealed clouding of the ethmoid and maxillary sinuses.

Immediately after the removal of a sequestrum from the left femur, the temperature rose to 102° and some fever persisted for three days.

The asthmatic attacks stopped immediately and did not recur up to the time of the patient's death 29 days later, following the development of a severe grade of granulocytopenia.

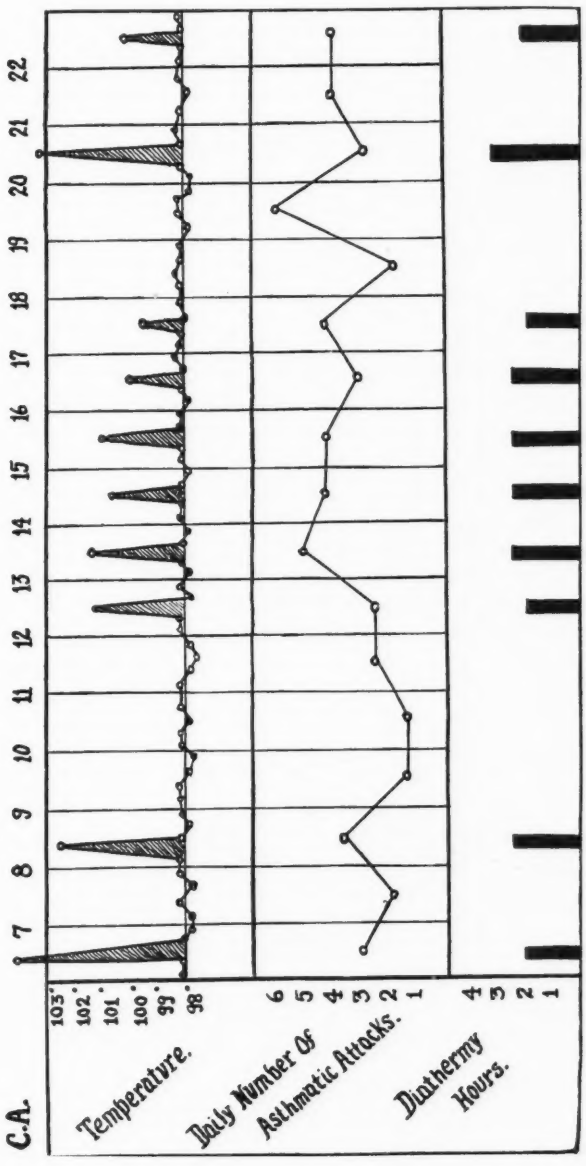


Fig. 7.—This chart represents the course of this patient's asthma (Case 6), during fever therapy. He was first given two treatments without any effect on the asthma. He was then given daily fever reactions for one week. Again the course of asthmatic paroxysms was uninfluenced. This patient received ten diathermy treatments in 17 days with fever ranging from 100° to 105° and lasting an average of three hours. During this time there was no relief of the asthma, if anything the attacks became more frequent.

Case 6.—C. A., a man, aged 45, had suffered from severe asthma, probably infectious in origin, for three years. The first attack followed influenza and pneumonia. There have been one or more attacks daily since then. Before the first admission to the hospital in 1930 there had been two nasal operations and a tonsillectomy without relief.

Attacks became more frequent, averaging from five to seven a day. There was temporary relief after a radical maxillary drainage in January, 1931. The following month attacks recurred as often as ten or twelve times a day. Further sinus drainage gave unsatisfactory results. Vaccine therapy failed to give relief. There was slight amelioration of attacks after the administration of "Felsol" and frequent injections of adrenalin.

Because all therapeutic measures had failed completely it seemed that this was an ideal case in which to try the effect of artificially induced fever therapy.

Since the inception of this work, three months ago, we have given a total of 44 treatments to 7 patients. Three of these patients (Cases 1, 2, and 3) were those in whom accidentally acquired infection produced relief from asthma during its duration and for a variable period thereafter. Despite this unusual opportunity to therapeutically induce fever in those who had previously been relieved by its accidental occurrence, we failed in a large measure to obtain a comparable therapeutic result.

One of these patients, over a period of two months, received 17 treatments, and he alone had fewer attacks and was convinced of material improvement in his asthmatic state. However, there were no complete remissions for more than 60 hours, and, in a disease as variable as bronchial asthma, nothing can be claimed for any therapeutic agent which does not achieve much more than this. The remaining patients obtained neither subjective nor objective relief.

We admit our technical inexperience and our undue concern, perhaps, for our patients who suffered great discomfort from the treatment even when narcotized with morphine.

While no conclusions, based on such a small group of cases, are permissible, it seems evident that spontaneous infection produces a nonspecific immunity reaction which differs in certain essential respects from that invoked by artificial means, and it seems equally obvious that fever per se is not the whole story.

There are no patients encountered in the practice of medicine who suffer more severely than the chronic asthmatic patients with upper respiratory infection and who are more difficult to treat. They wander from doctor to doctor, from clinic to clinic, from one climate to another, stopping long enough at each station to have another sinus operation, each time with transitory relief and almost inevitable recurrence. Any therapeutic procedure, provided it is reasonably safe and is based on rational thought, is worthy of thorough trial.

Fever artificially induced by mechanical means, offers a new therapeutic measure, which is worthy of more extensive clinical trial in certain types of chronic bronchial asthma.

REFERENCES

1. Chapman, Nathaniel: Quoted by Kern, R. A.: Problems in the Diagnosis and Treatment of Bronchial Asthma and Hay Fever, Atlantic M. J. **29:** 628, 1926.
2. Morris, A.: A Case of Hemiplegia Cured by an Attack of Fever, New Orleans Med. & Surg. J. **7:** 41, 1850.
3. Wagner-Jauregg, J.: Die Einwirkung der Malaria auf die progressive Paralyse Pschiac.-Neurol. Wchnschr. **20:** 132, 1918.
4. Schamberg, J. F., and Tseng, H.: Experiments on the Therapeutic Value of Hot Baths With Special Reference to the Treatment of Syphilis and Some Physiological Observations, Am. J. Syph. **11:** 337, 1927.
5. Carpenter, C. M., and Page, A. B.: The Production of Fever in Man by Short Radio Waves, Science **71:** 450, 1930.
6. King, J. C., and Cocke, E. W.: Therapeutic Fever Produced by Diathermy, With Special Reference to Its Application in the Treatment of Paresis, South. M. J. **23:** 222, 1930.
7. Feinberg, S. M., Osborne, S. L., and Afremow, M. L.: A New Method of Nonspecific Treatment of Allergic Disease. Preliminary Report, J. ALLERGY **2:** 291, 1931.

(For discussion, see page 503.)

HYPERTHERMIA INDUCED BY HIGH FREQUENCY ELECTRIC CURRENT IN THE TREATMENT OF INTRACTABLE ASTHMA*

HYMAN MILLER, M.D., AND GEORGE PINESS, M.D.
LOS ANGELES, CALIF.

EVER since the advent of malarial therapy for the production of controlled hyperpyrexia in paresis we have been intrigued with the possibility of applying the same method to the treatment of patients suffering from intractable asthma. However, we were restrained by a natural hesitancy in subjecting these individuals to so severe a procedure. With the announcement that hyperthermia could be produced by means of a new type of diathermy apparatus our interest was again aroused. We were, therefore, exceedingly gratified at the generous offer of the General Electric Company through Mr. W. V. Offutt of the use of such a machine.

Having the opportunity thus presented to us we were faced with the necessity of explaining to ourselves on just what theoretical grounds we would be justified in carrying out a procedure which involved subjecting already sick individuals to short periods of hyperthermia. Two well-known observations furnished the basis for our original desire to use this therapeutic measure: the first, that many chronic asthmatics experienced periods of freedom after a bout of fever, and the second that the parenteral administration of nonspecific protein with subsequent fever also frequently gave periods of relief. Of course, in considering the fever produced by diathermy the obvious question arose as to the significance of fever in itself in relation to the production of relief. Undoubtedly, the fever in both the above-cited observations is the result of reaction to foreign substances presumably protein in nature. Is it then the fever or the nonspecific action of the foreign protein which produces relief of symptoms? It is the general consensus of opinion that it is the latter. If so, then to what purpose the production of fever by diathermy if fever in itself is not responsible for relief of symptoms? For, as Bischoff[1] et al. have shown, in the fever produced by diathermy, it is questionable whether there is any significant destruction of body protein such as takes place in fevers of toxic origin. Moreover, even though it be proved that raising the body temperature by diathermy does cause a breaking down of body protein it must then be shown that this acts as does foreign protein in relieving the symptoms of asthma.

*Read before the Ninth Annual Meeting of the Association for the Study of Allergy, Philadelphia, June 8, 1931.

It must also be here noted that Bischoff et al. found that the production of fever by diathermy made the P_H of the blood more alkaline. Here, obviously, is another difference between artificial and natural fevers whose influence we could not foretell.

Such theoretical uncertainties we felt could be clarified only by subjecting a group of asthmatic patients to the type of fever we have been discussing. To justify this from the patient's point of view we felt that the procedure was essentially harmless as shown by the many reports of its use in the treatment of paresis. Further, it was determined to submit to this treatment only those patients who had no evidence of disease other than asthma, and lastly to treat only those patients who could properly be classified as intractable asthmatics, that is, those who in our opinion had run the gamut of every rational and many irrational methods of treatment without any considerable relief.

The following seven reports summarize the character of each case subjected to treatment, the degree and duration of hyperthermia produced and the response to treatment in terms of modification of symptoms.

CASE 1.—Mrs. M. F. S., aged forty-nine years.

Present Illness as given in May, 1921: Has had asthma since fifteen years of age. First attack occurred in summer while living in Kansas City, Missouri. Since then symptoms have persisted perennially, being aggravated by cold weather. The symptoms are characterized by more or less constant wheezing and cough, nasal coryza and obstruction. Came to California two years ago, since which time the more severe paroxysms have disappeared. The patient believes that contact with dogs and cats, or the eating of fish, cheese, milk, orange juice and chicken aggravates symptoms.

Past History: Tested five years ago and found non-sensitive. Polypoid tissue removed from the right posterior ethmoid and opening made into right antrum while under our observation.

Objective Finding: Swollen, completely occluding turbinates and swollen, sodden, pale nasal polypoid mucous membrane in the upper respiratory tract. Typical asthmatic breath sounds in the chest.

Laboratory Findings: Normal.

In June, 1929, the patient was tested intradermally to some 300 pollens, foods, epidermals and miscellaneous substances and found non-sensitive except to horse hair.

Course: Given potassium iodide. Treatment was instituted with stock mixed respiratory vaccine, ascending doses being given at weekly intervals beginning in September, 1929, and continued until November, 1929. The patient's condition did not improve during this period. An antigen containing horse dander was then administered, the final dose being given in February, 1931, when the patient reported

marked relief of symptoms. There was a relapse at the end of one month and despite resuming treatment with the epidermal antigen severe asthma persisted until the time of production of artificial fever.

Summary: A woman, aged fifty-one years, sensitive to horse hair, having had asthma perennially for thirty-six years had found little relief from change of climate, potassium iodide, several nasal operations and treatment over a period of almost two years with stock respiratory vaccine and epidermal antigen under our observation.

On March 28, 1931, the patient's temperature was raised by means of diathermy to 104.8° F.—40.4° C. (oral) over a period extending from 8:30 A.M. to 4 P.M. gradually dropping to 98° F.—36.6° C. (oral) at 8 P.M.

Weekly reports for seven weeks following treatment showed the usual variations of improvement and relapse characteristic of this patient's symptoms prior to the artificial fever.

CASE 2.—Miss E. S., aged thirty-five years.

Present Illness as given in July, 1929: Asthma since age of fifteen years. Onset in spring in San Francisco. Has never had a day of freedom since onset. Symptoms characterized by nonproductive cough, wheeze, dyspnea, usually worse at night. Fair relief from ephedrine.

Past History: Unessential.

Objective Findings: Boggy mucous membrane of the upper respiratory tract; chest hyperresonant with typical asthmatic breath sounds.

Laboratory Findings and X-ray Examination of the Chest: Normal.

In July, 1929, the patient was tested intradermally to about 300 pollens, foods, epidermals and miscellaneous substances, and found sensitive to several of each group.

Course: Despite specific therapy with pollen antigen and elimination of offending foods from September, 1929, until the date of production of artificial fever, the patient obtained only moderate relief, the symptoms being as persistent as before but somewhat less severe.

Summary: A woman, aged thirty-seven years, sensitive to foods, pollens and epidermals, having had asthma constantly for twenty-two years obtained only moderate relief from potassium iodide and specific therapy while under our observation for approximately two years.

On March 26, 1931, the patient's temperature was raised by means of diathermy to 103.8° F.—39.9° C. (oral) over a period extending from 8:30 A.M. until 10 A.M. gradually dropping to 99.7° F.— 37.6° C. (oral) at 8 P.M.

Weekly reports for seven weeks following treatment showed the usual variation of improvement and relapse characteristic of this patient's symptoms prior to the artificial fever.

CASE 3.—Miss E. T. A., aged forty years.

Present Illness as given in May, 1929: Asthma since an acute bronchitis in October, 1927, persistent and severe. Temporarily relieved by "Asthmador." Symptoms characterized by constant wheezing and dyspnea with frequent nocturnal, severe, acute paroxysms.

Past History: Lost thirty-nine pounds (17.7 kilograms) since onset of present illness. Now weighs seventy pounds (31.8 kilograms).

Treated by chiropractor for six months. Tooth removed two months ago.

Objective Findings: Emaciation. Marked congestion of mucous membrane of upper respiratory tract.

Laboratory Findings and X-Ray Examination of Chest: Normal.

In May, 1929, tested intradermally to some 300 pollens, foods, epidermals and miscellaneous substances and found non-sensitive.

Course: Given potassium iodide. In August, 1929, treatment with increasing doses of a stock vaccine of the mixed respiratory type was instituted. Marked local reactions occurred after the first few doses, and the patient reported considerable improvement. This was very temporary and up until the time of production of artificial fever the patient's condition remained essentially unchanged despite the continued administration of vaccine and potassium iodide.

Summary: A woman forty-two years of age, non-sensitive, has had persistent, severe asthma for three and one-half years despite treatment with stock respiratory vaccine and potassium iodide under our supervision for approximately two years.

On March 30, 1931, the patient's temperature was raised by means of diathermy to 105.6° F.—40.9° C. (oral) over a period extending from 8:30 A.M. to 1:10 P.M. gradually dropping to 97.2° F.—36.2° C. (oral) at 8 P.M.

Weekly reports for seven weeks following the hyperpyrexia showed the usual ups and downs of improvement and relapse but on the whole some improvement might be noted.

CASE 4.—Mrs. J. W. M., aged thirty years.

Present Illness as given in August, 1930: Persistent asthma for the past fourteen years. Better in summer but never entirely free. Symptoms characterized by attacks of sneezing, itching of ears, nose and throat, with coryza and nasal obstruction and almost constant wheezing, dyspnea and dry unproductive cough aggravated each night.

Past History: Came to California from Canada ten years ago with some resultant improvement. Had a tonsillectomy since coming to California without influencing symptoms.

Course Under Observation: In August, 1930, tested intradermally with some 300 pollens, foods, epidermals and miscellaneous substances. All tests were negative.

In November, 1930, treatment with increasing doses of a stock vaccine of the mixed respiratory type was instituted. Marked local reactions occurred after the first few doses and the patient reported considerable improvement which persisted until the time of the production of artificial fever, the vaccine administration being continued at weekly intervals.

Summary: A woman, thirty-one years of age, non-sensitive, having had persistent asthma for fifteen years despite several changes of climate, tonsillectomy and treatment with stock respiratory vaccine under our supervision for nine months was only slightly improved.

On March 27, 1931, the patient's temperature was raised by means of diathermy to 104.2° F.—40.1° C. (oral) over a period extending from 8:30 A.M. to 9:55 A.M. gradually dropping to 98.6° F.—37° C. (oral) at 4:30 P.M.

The patient reported weekly for seven weeks after this procedure and maintained the very marked improvement in her condition first noted within twenty-four hours after treatment. However, on the eighth week the patient reported that she had had several severe attacks of asthma.

CASE 5.—Mrs. S. S., aged forty years.

Present Illness as given in November, 1924: Intermittent asthma of eight years' duration. Constant for the last two years. Onset in Cleveland, relieved for a while on going to Arizona, recurred on coming to California two years ago. Symptoms characterized by wheezing, coughing and dyspnea, worse at night.

Past History: Unessential.

Objective Findings: Swollen, boggy, mucous membrane in the nose and throat. Typical asthmatic breath sounds with emphysema.

Laboratory Findings: Normal.

X-Ray Examination of Chest: Pleural Thickening.

In November, 1924, the patient was tested intradermally to some 300 pollens, foods, epidermals and miscellaneous substances and found slightly sensitive to only a few pollens. This has been checked many times since.

Course: Despite specific treatment to these from November, 1924, until the date of the production of artificial fever, relief could only be regarded as slight. Potassium iodide was administered at intervals.

Summary: A woman forty-seven years of age, slightly sensitive, has had persistent, severe asthma for fifteen years despite repeated change of climate, the administration of potassium iodide and specific treatment under our supervision for seven years.

On April 13, 1931, the patient's temperature was raised by diathermy to 103.2° F.—39.5° C. (axillary) over a period extending from 9 A.M. to 11 A.M. gradually dropping to 98° F.—36.6° C. (oral) at 4 P.M.

The patient was seen weekly for seven weeks after this procedure, reporting absolutely no amelioration of symptoms.

CASE 6.—Mr. A. J. G., aged thirty-seven years.

Present Illness as given in January, 1927: Asthma since the age of thirty-four years. Onset in December, 1924, while living in Detroit. Has since then had almost constant asthma with extremely severe paroxysms which at times have proved almost fatal. Came to Los Angeles one week prior to first visit at this office. Symptoms characterized by almost constant dyspnea with acute nocturnal paroxysms. One or two years before onset of above symptoms began to have violent sneezing spells, mostly in the evening.

Past History: Numerous operations on nose and throat.

Objective Findings: On physical examination the essential findings were: marked injection and hypertrophy of mucous membrane of the upper respiratory tract, and typical asthmatic breath sounds in the lungs.

Laboratory Findings: Normal.

X-Ray Examination of Chest: Normal.

In January, 1927, the patient was tested to some 300 pollens, foods, epidermals and miscellaneous substances and found sensitive to numerous members of each group.

Course: In January, 1927, specific pollen therapy and elimination of offending foods and environmental substances were instituted and persisted in until May, 1927, when patient left our observation, showing considerable improvement. From May, 1927, until February, 1930, the patient had several more nasal operations and took several trips to California and back to Detroit returning to us at the latter date with violent paroxysms of asthma. Retests confirmed previous findings, but despite the usual treatment little improvement was made in the patient's condition until the date of production of artificial fever.

Summary: A sensitive male, aged forty-one years, had had severe and, at times, almost fatal asthma for seven years despite several changes of climate, innumerable operations on nose and throat, administration of potassium iodide and specific treatment under our observation off and on for four years.

On March 20, 1931, the patient's temperature was raised by means of diathermy to 105° F.—40.5° C. (oral) over a period extending from 8:30 A.M. to 11:30 A.M. gradually dropping to 98.6° F.—37° C. (oral) at 9:30 P.M.

The patient was seen for seven weeks following this procedure during which time he had attacks of asthma as frequent and severe as he had ever experienced.

CASE 7.—Miss A. S., aged thirty-nine years.

Present Illness as given in November, 1924: Patient has had asthma for the past ten years. Onset in Chicago. Symptoms have persisted almost constantly since, despite coming to California eight years ago. Symptoms characterized by frequent so-called colds in the head, with sneezing, itching of the throat and eyes, wheezing and dyspnea, the latter symptoms relieved only by adrenalin.

Past History: Several operations on nose.

Objective Findings: Physical examination was negative except for boggy mucous membrane of the upper respiratory tract and typical asthmatic breath sounds in the chest.

Laboratory Findings and X-Ray Examination: Normal.

In November, 1924, tests were made intradermally to some 300 pollens, foods, epidermals and miscellaneous substances with negative results.

Course: In December, 1924, treatment with stock vaccine was instituted, increasing doses being given at weekly intervals until October, 1925, with considerable relief of symptoms. A relapse in June, 1926, was treated in the same manner until October, 1926. Returned in January, 1931, with severe asthma after having nasal polypi removed. Retests negative. "Campiodol" introduced into lung with considerable alleviation of symptoms and then relapse into severe asthma until date of production of artificial fever.

Summary: A non-sensitive woman, aged forty-six years, had had persistent asthma for seventeen years despite frequent changes of climate, several operations on nose and throat, the administration of potassium iodide, the introduction of "Campiodol" into the lung, and treatment with stock vaccine at intervals over a period of seven years under observation.

On March 19, 1931, patient's temperature was raised by means of diathermy to 104.2° F.—40.1° C. (oral) over a period extending from 11:45 A.M. to 3:30 P.M. gradually dropping to 98° F.—36.6° C. (oral) at 10:30 P.M.

During the month following this procedure patient showed a moderate amount of improvement, and it was decided to repeat the production of fever.

On April 14, 1931, patient's temperature was raised to 102.8° F.—39.3° C. (oral) over a period from 8:30 A.M. to 9:40 A.M. gradually dropping to 98.6° F.—37° C. (oral) at 4:30 P.M.

The patient was observed for six weeks after the above treatment and the marked relief of symptoms noted within twenty-four hours thereafter persisted, there being only occasional slight attacks of wheezing.

To draw conclusions from so small a series is scarcely warranted. Particularly is this so since we feel that the periods of fever should have been of longer duration and probably repeated on several successive days in order to simulate properly an endogenous fever as in case number six. These reports are therefore offered only as suggesting a new trend of investigation and as stimulating further attempts to find relief for the intractable asthmatic.

REFERENCE

1. Bischoff, F., Ullman, H. J., Hill, E., and Long, M. L.: Studies in Hyperthermia Induced by the High Frequency Electric Current, J. Biol. Chem. **85**: 675, 1930.
Idem. **90**: 321.

(For discussion, see page 503.)

A STUDY OF THE REACTIONS IN NON-SENSITIVE SKIN OF MIXTURES IN VITRO OF REAGIN AND ATOPEN*†

FRANCIS L. FORAN, M.D., AND MEYER R. LICHTENSTEIN, M.D.
CHICAGO, ILL.

THE viewpoint that mixtures of hypersensitive serum with its homologous atopen are neutralized in the test tube and do not cause specific atopic reactions in nonsensitive skin seems to be held by all investigators of the subject with the exception of Gay and Chant.

Coca and Grove[1] (1924) and Levine and Coca[2] (1925) demonstrated the failure of such mixtures to sensitize a normal skin site to the subsequent injection of the atopen, and, on the other hand, the unimpaired activity of the atopen in the mixtures to cause reaction in a site previously sensitized by serum alone. They concluded that "reagin is neutralized, that is, deprived of its sensitizing power by the admixture (in vitro) of the atopen, but that the activity of the latter is not lessened in any appreciable degree." They argued, therefore, for a unilateral neutralization of reagin, and not of atopen.

These authors appreciated the alternative possibility of neutralization of the mixture with accompanying specific atopic reaction in the skin of the transfer subject. Such apparent reactions were noted but were discounted on the ground that they "were not larger than those produced with mixtures of serum and saline solution." These controls, however, do not appear in the protocols as published.

Clarke and Gallagher[3] (1926) in a study of the effect of separate injection in the same site of atopen and serum at a five minutes' spacing, asserted that neutralization can occur in the skin without specific atopic reaction and that the reagin must have an opportunity to act upon the cell before coming in contact with the atopen. Baldwin[4] (1930) reported that homologous mixtures in the test tube produced no larger reactions than controls, but noted many exceptions. M. Walzer,[5] in discussion, while agreeing with Baldwin, added that there is a difference in the skin reactivity of neutralized and unneutralized mixtures; he implied that some mixtures in vitro do react upon intradermal injection due to an incomplete neutralization in the test tube.

Gay and Chant[6] (1927) using a numerical measure of reactions concluded that homologous mixtures were in definite contrast to the controls and suggested that neutralization does not become complete until after injection into the normal tissues. They made their readings

*From the Allergy Clinic, Rush Medical College.
†Presented at the meeting of the Chicago Society of Allergy, April 20, 1931.

at fifteen minutes; the other investigators do not state the time interval, but apparently looked for almost immediate reaction.

It is obvious that the simple but crucial question of the reaction of mixtures in the test tube upon intradermal injection into nonsensitive skin is still debatable. Our experiment leads us to believe that such mixtures do not interact in the test tube and do cause a specific atopic reaction in nonsensitive skin.

It would seem that much of the confusion has arisen from the methods and inherent difficulties of the experiment. Reactions were not noted in a sequence of definite time intervals; and it has been difficult to express them as objective values. Dealing with so variable a criterion as the skin test, recently discussed by Alexander and McConnell,[7] we believe that a constant tendency of reactions can be determined only by a method permitting the averaging of large numbers of closely controlled comparisons.

Our procedure is as follows. Measurement of the square surfaces of wheal and erythema areas is made by a method developed several years ago by one of us (F. L. F.). The areas are outlined in ink and transferred to cross-section tracing paper treated with a transparentizing fluid.* The areas can then be rapidly estimated in units of the small squares included; this number may, if desired, be translated to square millimeters by multiplying by 1.6. In this experiment, however, we established the relative proportion of the wheal and erythema areas by giving to one control site a value of 1.0; the separate wheal and erythema ratios are then combined in one mean ratio. The reactions are thus given a simple objective numerical expression proportionate to their intensity. An example of this procedure is submitted in Table I; other tables will contain only the numerical ratios of the square surfaces of the reaction areas.

This plan of experiment furnishes two homologous mixtures, Sites II and III, and two nonhomologous mixtures, Sites I and IV. There are thus afforded two comparisons of homologous mixtures with control mixtures of the same serum and nonhomologous atopen, Site II/ Site I and Site III/ Site IV; and two comparisons of homologous mixtures with control mixtures of the same atopen and nonhomologous serum, Site III/ Site I and Site II/ Site IV.

Furthermore, the four ratios elicited permit a ready comparison between any two sites, and their relation or ratio may be expressed in a simple numeral, the quotient: e.g., in the ninety-minute reading Site III/ Site IV = 11.7/ 1.7 = 6.9. A series of such ratios may then be averaged by obtaining the mean of their several quotients: e.g., the sum of 27 such quotients equaling 167.7, a mean value of 6.2 is

*The materials, cross-section tracing paper 318-0, and "Primo" transparentizing fluid are obtainable at the Frederick Post Co., 316 South Wabash Avenue, Chicago, Ill.

TABLE I

SITE	MIXTURE	15 MIN. READING			60 MIN. READING			90 MIN. READING		
		WHEAL AREA (RATIO)	MEAN RATIO OF AREAS	ERYTH. AREA (RATIO)	WHEAL AREA (RATIO)	MEAN RATIO OF AREAS	ERYTH. AREA (RATIO)	WHEAL AREA (RATIO)	MEAN RATIO OF AREAS	ERYTH. AREA (RATIO)
I.	B-wheat ser.	30	1.0	148	8	1.0	8	6	1.0	6
	Rag. At.	(1.0)		(1.0)	(1.0)		(1.0)	(1.0)		(1.0)
II.	B-wheat ser.	26	0.9	134	30	8.8	113	31	9.6	85
	B-w. At.	(0.9)		(0.9)	(3.7)		(14.0)	(5.1)		(14.2)
III.	Ragweed ser.	28	1.4	270	30	13.7	190	28	11.7	113
	Rag. At.	(0.9)		(1.9)	(3.7)		(23.7)	(4.7)		(18.8)
IV.	Ragweed ser.	26	*0.9	121	31	8.2	100	10	1.7	10
	B-w. At.	(0.9)		(0.9)	(3.9)		(12.5)	(1.7)		(1.7)

Site I. J. S. serum (buckwheat sensitive) 1/5 dilution, 0.9 c.c. Giant ragweed extract, 0.1 c.c.
Site II. J. S. serum as in Site I. Buckwheat protein solution, 0.1 c.c.
Site III. A. B. serum (ragweed sensitive) 1/5 dilution, 0.9 c.c. Giant ragweed extract, 0.1 c.c.
Site IV. A. B. serum as in Site III. Buckwheat protein solution, 0.1 c.c.
Subject I. A. Age of mixture, five days. Incubation at 37° C., two hours.

To further illustrate the procedure of obtaining the ratios of the reacting areas the ninety-minute reading of Table I is detailed thus:

SITE	COLUMN A		COLUMN B		COLUMN C
	Areas in units of square surface as read from graphs.		Ratio of square surfaces of Col. A in values of Site I as 1.0.		Mean ratio of reacting areas by combining the wheal and erythema ratios of Col. B.
	Wheal	Erythema	Wheal	Erythema	
I	6	6	1.0	1.0	1.0
II	31	85	5.1	14.2	9.6
III	28	113	4.7	18.8	11.7
IV	10	10	1.7	1.7	1.7

established. Thus the general tendency of any series of similar reactions may be condensed to the expression of a single numeral.

Twenty-two transfer subjects were used. With one exception to be commented upon later, all were negative to the atopens used in the experiment and had no known hypersensitiveness to other atopens. Ten, however, had histories strongly suggestive of allergy. Ten hypersensitive sera were used. The blood was allowed to clot, the serum pipetted off, centrifuged to remove cells, and preserved by adding one volume of Merthiolate 1 to 1,000 dilution to three volumes of serum. With few exceptions the serum was diluted with saline to a one-to-five concentration and 0.9 c.c. of this dilution added to 0.1 c.c. of atopen solution; of these mixtures, 0.02 c.c. were injected intradermally. Ten mixtures of serum with homologous atopen and thirteen mixtures of

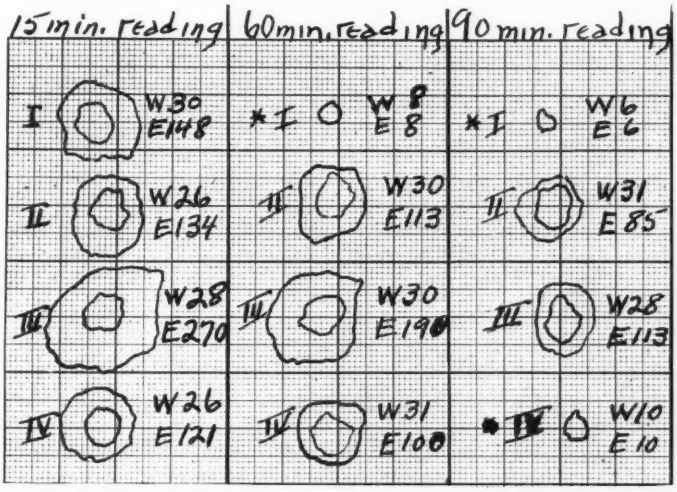


Fig. 1.—Graphs of reactions charted in Table I. W, wheal; E, erythema. In some control sites the late readings showed no distinct erythema. In such cases we made the practice of recording an erythema reaction as coextensive with the wheal area, designated by (*).

serum with nonhomologous atopen were employed. Tests were made with mixtures of various ages: freshly made, 5 tests; at two to five hours, 14 tests; at twenty-four hours, 12 tests; at two to four days, 3 tests; at five to nine days, 15 tests; at twenty-six days, 2 tests.

The majority of the mixtures were kept in the refrigerator and incubated one hour at 37° C. before succeeding tests. The total of such fractional incubations at 37° C. varied from one to six hours. Four mixtures aged at room temperature for one to forty-eight hours were tested on 12 of the transfer subjects. The results with the mixtures subjected to the longer aging and incubation periods conformed to the general tendency of the experiment.

Six atopen solutions were used: Giant ragweed and timothy, each 1.5 mg. nitrogen per c.c.; buckwheat, 5 mg. protein per c.c.; wheat,

2.5 mg. protein per c.c.; house dust, a highly active extract of undetermined nitrogen content; insulin, the manufacturers' U-40.

Each homologous mixture of serum and atopen was, with few exceptions, due to loss of material, doubly controlled by both a mixture of the serum with a nonhomologous atopen and a mixture of the atopen with a nonhomologous serum subjected to the same conditions of aging and temperature. The control mixtures were always injected about 3 cm. below the antecubital fold and the homologous mixture about 5 cm. below the controls.

The tables submitted are typical examples from our protocols. They are selected to show both the general trend of our experiment and the discrepancies of some protocols, due to unavoidable experimental variations.

TABLE II

SUBJECT	SITE	AGE OF MIXTURE	INCUB. AT 37° C.	RATIO OF SQUARE SURFACES OF REACTION AREAS AT:		
				15 MIN.	60 MIN.	90 MIN.
R. B.	I.	1 day	1 hour	1.0	1.0	1.0
	II.	1 day	1 hour	0.4	0.3	0.4
	III.	1 day	1 hour	0.9	1.0	1.1
	IV.	1 day	1 hour	0.3	0.06	0.1
J. F.	I.	1 day	1 hour	1.0	1.0	1.0
	II.	1 day	1 hour	1.0	3.3	7.9
	III.	1 day	1 hour	1.7	5.2	13.5
	IV.	1 day	1 hour	0.7	0.7	1.6

Site I: J. S. serum (buckwheat sensitive) 1/5 dil., 0.9 c.c. Giant ragweed ext., 0.1 c.c.
Site II: J. S. serum as in Site I. Buckwheat protein solution, 0.1 c.c.
Site III: A. B. serum (ragweed sensitive) 1/5 dil., 0.9 c.c. Giant ragweed ext., 0.1 c.c.
Site IV: A. B. serum as in Site III. Buckwheat protein solution, 0.1 c.c.

Table II charts experiments with the same mixtures as used in Table I. By an oversight, a subject, R. B., was used who was found sensitive to ragweed extract. It will be noted that the control site I and the homologous mixture site III, both containing ragweed atopen, maintained a ratio of approximate unity in all three readings; this is in sharp contrast to the advancing ratios noted for the same sites in subjects I. A., Table I, and J. F., in Table II. It thus furnishes a confirmation of the demonstration by Coca and his coworkers that atopen at least is not neutralized by admixture with its corresponding serum. On the other hand it should be observed that, concurrently with the above, site II, an homologous mixture with buckwheat atopen to which R. B. was not sensitive, shows a ratio to control site IV expressed by the quotient 5 at sixty minutes, and 4 at ninety minutes.

Table III is an example of the readings obtained with strongly atopic sera; in the subject M. O. the mixtures had been subjected to the longest aging and incubation in our experiment. As might be expected, results did not always conform to a general pattern. In

Table IV will be observed control sites which exceed the homologous mixture sites at sixty and ninety minute readings. Neither serum used was strongly atopic. Results such as these are very misleading unless counterbalanced in the averaging of a large series of reactions.

In Table V, a strongly atopic serum is paired with a weak serum and the atopen concentration increased eightfold with the thought that a

TABLE III

SUBJECT	SITE	AGE OF MIXTURE	INCUB. AT 37° C.	RATIO OF SQUARE SURFACES OF REACTION AREAS AT:		
				15 MIN.	60 MIN.	90 MIN.
A. C.	I.	5 days	2 hours	1.0	1.0	1.0
	II.	5 days	2 hours	1.3	12.9	21.3
	III.	5 days	2 hours	1.8	13.2	18.4
	IV.	5 days	2 hours	2.2	7.0	3.1
M. O.	I.	26 days	6 hours	1.0	--	1.0
	II.	26 days	6 hours	Lost by spillage		
	III.	26 days	6 hours	1.4	--	6.0
	IV.	26 days	6 hours	4.8	--	2.8

Site I: A. P. serum (dust sensitive) 1/5 dil., 0.9 c.c. Giant ragweed ext., 0.1 c.c.
Site II: A. P. serum as in Site I. House dust ext., 0.1 c.c.
Site III: S. G. serum (ragweed sensitive) 1/5 dil., 0.9 c.c. Giant ragweed ext., 0.1 c.c.
Site IV: S. G. serum as in Site III. House dust ext., 0.1 c.c.

TABLE IV

SUBJECT	SITE	AGE OF MIXTURE	INCUB. AT 37° C.	RATIO OF SQUARE SURFACES OF REACTION AREAS AT:		
				15 MIN.	60 MIN.	90 MIN.
C. S.	I.	4 days	2 hours	1.0	1.0	1.0
	II.	4 days	2 hours	1.0	1.3	1.1
	III.	4 days	2 hours	0.9	1.4	0.8
	IV.	4 days	2 hours	1.1	1.6	1.0
I. B.	I.	8 days	3 hours	1.0	1.0	1.0
	II.	8 days	3 hours	0.7	0.9	1.7
	III.	8 days	3 hours	0.7	1.1	1.9
	IV.	8 days	3 hours	0.7	1.2	1.3

Site I: H. V. serum (wheat sensitive) 1/5 dil., 0.9 c.c. Insulin U-40, 0.1 c.c.
Site II: H. V. serum as in Site I. Wheat protein solution, 0.1 c.c.
Site III: M. C. serum (insulin sensitive) 1/5 dil., 0.9 c.c. Insulin U-40, 0.1 c.c.
Site IV: M. C. serum as in Site III. Wheat protein solution, 0.1. c.c.

TABLE V

SUBJECT	SITE	AGE OF MIXTURE	INCUB. AT 37° C.	RATIO OF SQUARE SURFACES OF REACTION AREAS AT:		
				15 MIN.	60 MIN.	90 MIN.
I. G.	I.	1 day	1 hour	1.0	1.0	1.0
	II.	1 day	1 hour	4.0	8.9	12.7
	III.	1 day	1 hour	2.0	4.7	5.1
	IV.	1 day	1 hour	4.8	8.7	5.9
L. Z.	I.	5 days	2 hours	1.0	1.0	1.0
	II.	5 days	2 hours	0.9	18.0	27.2
	III.	5 days	2 hours	0.7	4.1	6.7
	IV.	5 days	2 hours	1.3	6.7	7.8

Site I: A. P. serum (dust sensitive) no dil., 0.1 c.c. Insulin U-40, 0.4. c.c.
Site II: A. P. serum as in Site I. House dust ext., 0.4 c.c.
Site III: M. C. serum (insulin sensitive) no dil., 0.1 c.c. Insulin U-40, 0.4 c.c.
Site IV: M. C. serum as in Site III. House dust ext., 0.4 c.c.

possible saturation of reagin might affect our result. Here, it is true that the homologous mixture in site III reacts somewhat less than the control in site IV. This must be interpreted with recognition of the nonspecific irritation of the strong dust extract as shown by a comparison of the two control sites I and IV. Site III, however, shows a wide ratio to its other control in site I; and the homologous dust mixture in site II reacts in sharp contrast to both control sites I and IV.

SUMMARY

An analysis of the total protocol yields the following:

1. In 49 tests, mixtures of hypersensitive serum with its homologous atopen were compared with control mixtures of the same serum with nonhomologous atopen and the ratio of specific to control reactions

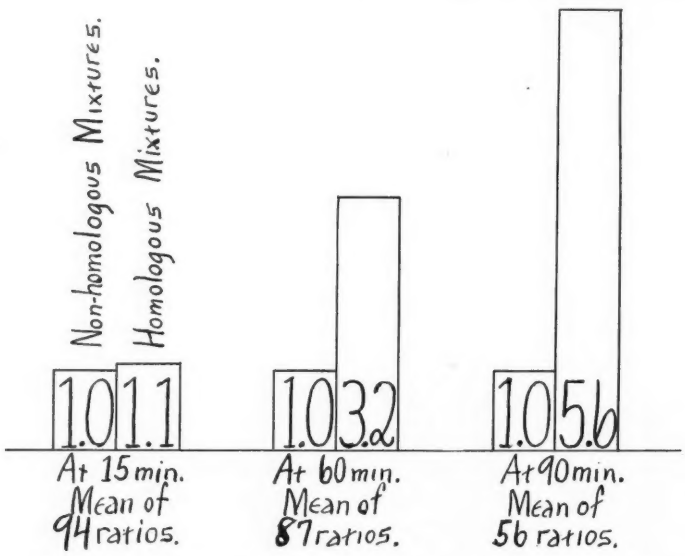


Fig. 2.—Diagram of the mean ratios of the square surfaces of the reaction areas of homologous and nonhomologous serum-atopen mixtures.

was expressed as a quotient. It followed that: (a) Of 49 such ratios at fifteen minutes' reading, the ratio was greater than unity in 19; equal or less than unity in 30; and the mean of the 49 ratios was 1.2. (b) Of 46 such ratios at sixty minutes' reading, the ratio was greater than unity in 36; equal or less than unity in 10; and the mean of the 46 ratios was 3.4. (c) Of 27 such ratios at ninety minutes' reading, the ratio was greater than unity in 20; equal or less than unity in 7; and the mean of the 27 ratios was 6.2.

2. In 45 tests, mixtures of atopen with its homologous serum were compared with control mixtures of the same atopen with nonhomologous serum. It followed that: (a) Of 45 such ratios at fifteen minutes' reading, the ratio was greater than unity in 20; equal or less than

unity in 25; and the mean of the 45 ratios was 1.1. (b) Of 41 such ratios at sixty minutes' reading, the ratio was greater than unity in 27; equal or less than unity in 14; and the mean of the 41 ratios was 3.0. (c) Of 29 such ratios at ninety minutes' reading, the ratio was greater than unity in 22; equal or less than unity in 7; and the mean of the 29 ratios was 5.5.

Combining these two groups the mean ratio of specific to control reactions is thus established for 94 ratios at fifteen minutes' reading, of approximately 1.0; for 87 ratios at sixty minutes' reading, of approximately 3.0; and for 56 ratios at ninety minutes' reading, of approximately 6.0.

COMMENT

The general tendency of homologous mixtures, subjected to wide variations of aging, temperature, and dilution, to produce reactions in non-sensitive skin so distinctly preponderant over their controls would seem to eliminate neutralization in the test tube, in the sense of the destruction of the specific properties of either reagin or atopen. But what is the positive significance of these results?

It is repeatedly stated or implied that a specific atopic reaction of mixtures in the normal skin would indicate the formation in the test tube of some toxic interaction product. This is a possible but not a necessary hypothesis. Reactions of the time incidence noted in our investigation are more easily explainable on the hypothesis that atopen and reagin mixtures are inert in the test tube and that interaction occurs only in the presence of some tissue factor. Coca and Grove observed that a definite incubation of sensitizing serum in the skin site was needed before the subsequent injection of atopen would satisfactorily demonstrate a transfer of hypersensitiveness. In our report, it has been noted that a ratio of practical unity at fifteen minutes advances to a wide divergence at ninety minutes. We suggest that the specific reactions we obtained are not due to some toxin preformed in the test tube but depend on the sensitization of the normal tissue by the unchanged reagin in the mixture and subsequent reaction with the accompanying atopen. In other words, it would not differ from the Prausnitz-Küstner phenomenon, except for the indifferent point of separate or simultaneous injection of reagin and atopen. The hypothesis of a toxic product in the test tube necessitates the unnecessary and complicating assumption of a highly stable toxic compound and some additional explanation for the delayed appearance of skin reaction.

CONCLUSIONS

1. Mixtures in vitro of hypersensitive serum with homologous atopen do react upon injection in non-sensitive skin.

2. Neutralization of such mixtures, i.e., destruction of the specific properties of either reagin or atopen, does not occur in the test tube.

3. The reagin and atopen in such mixtures are probably inert in the test tube and react only after injection, in the presence of some tissue factor.

4. The reaction of such mixtures does not essentially differ from the Prausnitz-Küstner phenomenon.

REFERENCES

1. Coca, A. F., and Grove, E.: J. Immunol. **10**: 445, 1925.
2. Levine, P., and Coca, A. F.: J. Immunol. **11**: 411, 1926.
3. Clarke, J. A., and Gallagher, M. G.: J. Immunol. **12**: 461, 1926.
4. Baldwin, L. B.: J. ALLERGY **1**: 438, 1930.
5. Walzer, M.: J. ALLERGY **1**: 464, 1930.
6. Gay, L. M., and Chant, E.: Bull. Johns Hopkins Hosp. **40**: 270, 1927.
7. Alexander, H. L., and McConnell, F. S.: J. ALLERGY **2**: 23, 1930.

THE EFFECT OF ALLERGY ON ALLERGEN ABSORPTION FOLLOWING PARENTERAL INJECTIONS*

MILTON B. COHEN, M.D., E. E. ECKER, PH.D., AND J. A. RUDOLPH, M.D.
CLEVELAND, OHIO

IN PREVIOUS studies we have demonstrated a delay in the appearance of ragweed allergen in the blood after spraying ragweed pollen material into the noses of allergic individuals.[1] The absorption time of the nonallergic individual varied from 14 to 31 minutes, while that of the allergics ranged from a positive reaction in 47 minutes to no reaction after two hours. We have also shown that in eight out of ten nonallergic subjects the allergen could be demonstrated in the blood for 24 hours but in no case was there any demonstrable at the end of 48 hours.[2]

These results led us to the question as to whether or not the same phenomenon holds true in the case of parenteral inoculations. The present report deals with this particular phase of the problem.

METHOD

An area of the skin in the upper arm was passively sensitized with the serum of the same ragweed-sensitive subject employed in our earlier studies, on 11 allergic (nonragweed sensitive) subjects and on 12 normal controls. The serum was obtained under strict aseptic precautions and only unheated serum was used. The reason for the use of unheated serum is based on the work of Chant and Gay[3] who showed that sera heated for 30 minutes at 56° C. gave rise to a definite and immediate skin reaction. The serum was used fresh since Chant and Gay also pointed out that sera kept at ice box temperature for a period of 12 days or more were apt to give similar positive reactions. We preferred this particular serum, first, because of the uniformity of its reactions and secondly, because Walzer and Bowman[4] recently showed that allergic patients did not accept passive local sensitization with the same regularity or to the same degree as the normal individual. Therefore, the nature of the sensitizing serum should be reckoned with in passive local sensitizations. In all our negative cases we have carefully determined that the individual accepted passive transfer in high dilution. The reactions in this study were induced 24 hours after the local sensitizing injection by subcutaneous administration of 0.1 c.c. of 5 per cent extract of ragweed pol-

*From the Institute of Pathology, Western Reserve University, Cleveland, Ohio.
Read before the Ninth Annual Meeting of the Association for the Study of Allergy, Philadelphia, June 8, 1931.

len into the opposite arm. The extracts were glycerolated (50 per cent) and contained equal parts of the reactive components of short and giant ragweed pollens. The skin test areas were observed for the appearance of the typical allergic wheal which is characteristic of the Prausnitz-Küstner reaction when the allergen is injected directly into the passively sensitized area. In all instances the area of subcutaneous injection was carefully examined for evidences of local reaction so as to exclude the possibility of slight ragweed sensitivity in the test subjects, and controls with normal serum were used. In no instance was a local reaction observed at the site of the subcutaneous injection.

Table I shows the results obtained in 11 allergic (nonragweed sensitive) and 12 normal subjects.

TABLE I

SPEED OF ABSORPTION OF RAGWEED POLLEN MATERIAL FOLLOWING PARENTERAL INOCULATIONS

CASE NUMBER (NORMALS)	APPEARANCE TIME IN MINUTES	CASE NUMBER (ALLERGICS)	ALLERGIC TO	APPEARANCE TIME IN MINUTES
1	+ in 19	1	Dust	0 in 78
2	+ in 22	2	House dust	0 in 70
3	+ in 43	3	Dust	0 in 65
4	+ in 20	4	Dust and egg	0 in 60
5	+ in 16	5	Dust	0 in 95
6	+ in 20	6	Dust	0 in 90
7	+ in 21	7	Dust	+ in 54
8	+ in 13	8	Dust	0 in 64
9	+ in 24	9	Dust	+ in 40
10	+ in 18	10	Food and bacteria (?)	+ in 40
11	+ in 24	11	Dust and slight	0 in 60
12	+ in 20		sensitivity to ragweed (?)	

From these results it is once more evident that the speed of reaction in the normals is far greater than that in the allergic subjects, with the exception of one individual in the normal series whose reaction time was 43 minutes. This is in accordance with the work of Gay and Chant.[5] All the others reacted within 13 to 24 minutes. In the allergic series, however, only three reacted in resp: 54, 40 and 40 minutes, while the others failed to react during the periods recorded. As stated above, all those in whom reactions were negative were tested with dilutions (1:5000) of ragweed pollens similar to those giving reactions with this test serum in normals and all reacted well.

DISCUSSION

In our previous work on absorption through the nasal mucous membrane we did not study the mechanism of the delayed reaction. This type of reaction may be due to changes in the absorption rate through the mucous membrane per se, to some submucosal (parenteral) mechanism or to variations in the capacity of these individuals to accept

passive transfer. The control studies performed on these subjects convinced us that the variations were too large to be explained on differences in passive transfer acceptance, because all reacted in the passively sensitized areas with dilutions of ragweed 1:5000.

Since the results following subcutaneous administration of pollen parallel so closely those following its nasal administration, changes in the nasal mucosa can be ruled out as the cause for the delay. It would seem, therefore, that the mechanism is parenteral and may be similar to the phenomenon noted by Opie[6] in his studies on the absorption of antigens following repeated inoculations. He showed that in sensitive animals the antigen is fixed at the site of injection and may be recovered in large part from inflamed and necrotic tissue. In Opie's experiments the Arthus phenomenon (inflammatory reaction at the site of injection after repeated inoculations of the antigen) was produced. In none of our studies was there any local reaction at the site of the subcutaneous injections so that this mechanism cannot entirely explain our results in allergic subjects not sensitive to the allergen employed. When allergic individuals are tested with the allergen to which they are specifically sensitive, local reactions similar to Arthus phenomenon occur and give rise, for example, to the nasal symptoms in hay fever. In several such individuals we have been unable to demonstrate ragweed allergen in the blood within three hours following its nasal administration.[1] Whether the symptoms of allergy at the site of entrance of the allergen can be interpreted solely as an Arthus phenomenon must be determined by further investigations.

CONCLUSION

There is a marked delay in the reactions to ragweed pollen material in passively sensitized areas of the skin of allergic individuals not sensitive to ragweed pollen material following the parenteral injection of ragweed pollen extract.

REFERENCES

1. Cohen, M. B., Ecker, E. E., Breitbart, and Rudolph, J. A.: J. Immunol. **18:** 419, 1930.
2. Cohen, M. B., Ecker, E. E., and Rudolph, J. A.: J. ALLERGY **1:** 529, 1930.
3. Chant, E., and Gay, L. B.: Johns Hopkins Hosp. Bull. **40:** 63, 1927.
4. Walzer, M., and Bowman: Proc. Soc. Exper. Biol. & Med. **28:** 423, 1931.
5. Gay, L. B., and Chant, E.: Johns Hopkins Hosp. Bull. **40:** 270, 1927.
6. Opie, E. L.: J. Immunol. **8:** 55, 1923; J. Exper. Med. **39:** 659, 1924.

(For discussion, see page 502.)

ECONOMIC RESULTS FROM THE TREATMENT OF POLLEN ASTHMA AND HAY FEVER

LESLIE N. GAY, M.D.*
BALTIMORE, MD.

THE results obtained from the treatment of hypersensitive patients suffering with hay fever and asthma, caused by pollen inhalation, have been reported by a number of investigators during the past decade. Attention is directed particularly to the favorable reports of Walker,[1] Cook and Vander Veer,[2] Caulfield,[3] Vander Veer,[4] Rackemann,[5] Ramirez[6] and Piness.[7] Rackemann[5] summarizes in a comparative table percentage results as follows:

	PERCENTAGE RESULTS CONSOLIDATED		
	PERFECT	SATISFACTORY	POOR
Cook and Vander Veer	12	52	36
Vander Veer	23	49	28
Walker	25	52	23
Rackemann	10	66	24

These investigations are extremely important contributions from the symptomatic standpoint, but an accurate tabulation of results on an economic basis has not as yet been published. With this in mind, therefore, I have attempted to obtain from patients in the Protein Clinic of the Johns Hopkins Hospital and in private practice a daily record of symptoms during the three years 1927, 1928 and 1929. The patient decided whether the day was "bad," as estimated by the persistence of continuous symptoms throughout the twenty-four hours; or whether the day was "poor" as estimated by an hour or two of symptoms during the twenty-four hours. A "good" day is a day during which period the patient had no symptoms.

METHOD

When the patient began treatment, a card was given to him with a simple code, to be used in the recording of the symptoms which might ensue during the season. The advantage of this procedure is that it provides a record made currently, and at the end of the season one is not at all dependent on the patient's memory, nor is the physician's opinion a part of the appraisal. (Charts 1 and 2.)

The extracts used in the diagnosis and treatment of these patients were prepared in the laboratory of the Johns Hopkins Hospital ac-

*From the Protein Clinic of the Medical Dispensary of the Johns Hopkins Hospital.

cording to the technic of Coca.[8] Because of the presence of large quantities of giant ragweed in Maryland, the ragweed pollen sensitive patients were treated with a solution containing equal parts of short and giant ragweed extracts. In the treatment of grass pollen sensitive sufferers, the solutions which were used in treatment contained the extract of the predominating timothy pollen combined with an extract of orchard grass pollen, or if indicated, with the extract of the pollen of English plantain. The last-mentioned grass is,

AT THE END OF THE SEASON PLEASE RETURN THIS CARD TO:—

DAILY RECORD OF SYMPTOMS

Name _____ Year _____

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
March																															
April																															
May																															
June																															
July																															
Aug.																															
Sept.																															
Oct.																															

Chart 1.—Specimen card used by patients in recording symptoms during the pollen period.

EXPLANATION

At the end of each day please record the degree of symptoms of hay fever or asthma.

Code:

Good day	No mark
Poor day	
Hay fever	.
Asthma	⊙
Bad day	
Hay fever	×
Asthma	⊗

By a bad day is meant the occurrence of more or less continuous symptoms.

By a poor day is meant the occurrence of symptoms, morning or evening for from one to two hours.

Total No. Poor Days:—

Total No. Bad Days:—

Chart 2.—Reverse of card shown in Chart 1.

of course, in an entirely different botanical genus and is as specific as is either ragweed or timothy in the treatment of the hypersensitive individual.

The same method of administering treatment to the patients was used for the three years. The patient received treatment three times each week; the dosage was begun at the level of safety and gradually increased until concentrated pollen extract was injected. As a number of the patients in this report suffered with multiple pollen sensitiveness, having not only spring hay fever or asthma (grasses) but the summer hay fever or asthma (ragweeds) as well, the scheme as outlined in Table I exemplifies the method used in the treatment of all classes of patients.

Treatment was commenced in March or in June depending upon the group into which each patient fell, determined by the history obtained from the patient and by the intradermal reaction to specific pollens. The concentration and quantity of extracts used in treatment were increased with caution; rarely was the dose double the quantity given at the preceding treatment. Treatment was concluded when it was found by the exposure of plates that the specific pollen was out of the atmosphere. By this scheme, empiric though it is, reactions of a serious nature have been avoided in the clinic since its beginning in 1919.

The local reaction at the site of injection depends entirely on the depth to which the needle is injected. An injection into the deep tissue of the deltoid rarely produces redness; the same volume and concentration of extract, if given into the superficial tissue, will produce a large wheal surrounded by extensive erythema and at the same time the patient complains of intense itching. This type of reaction does not apply only to pollen extracts for with tuberculin similar conditions can be produced. In the treatment of ocular tuberculosis a violent local reaction can be produced if the tuberculin is injected into the superficial layers of the skin over the deltoid muscle. A similar dose injected into the deeper tissue is absorbed without the slightest local reaction. I[9] do not agree with the rather general opinion that the subsequent doses of pollen extract depend upon the local reaction arising at the site of injection from the previous treatment.

The results of this method of treatment, carried out over a period of three years, are extremely interesting, especially because in 1928 the atmospheric pollen saturation was maximum and symptoms were correspondingly severe, while 1927 and 1929 were average seasons.

In attempting to estimate the economic results of treatment certain assumptions must be made which cannot be absolutely substantiated. For example, one cannot say with certainty that a patient would have forty-two days of discomfort if he failed to take treatment. Therefore, in the consideration of the results of treatment,

TABLE I

OUTLINE OF A COURSE OF TREATMENT FOR A TYPICAL SPRING-SUMMER TYPE OF HAY FEVER OR BRONCHIAL ASTHMA DUE TO POLLENS

DATE	DOSAGE		
March			
30 Given	0.1 c.c.	1:10,000	TIMOTHY
April			
1 "	0.25 c.c.	"	
4 "	0.4 c.c.	"	
6 "	0.6 c.c.	"	
8 "	0.8 c.c.	"	
11 "	0.15 c.c.	1:1000	
13 "	0.2 c.c.	"	
18 "	0.35 c.c.	"	
20 "	0.5 c.c.	"	
22 "	0.7 c.c.	"	
25 "	0.9 c.c.	"	
28 "	0.15 c.c.	1:100	
29 "	0.2 c.c.	"	
May			
3 "	0.35 c.c.	"	
7 "	0.5 c.c.	"	
9 "	0.7 c.c.	"	
11 "	0.9 c.c.	"	
13 "	0.15 c.c.	1:10	
16 "	0.2 c.c.	"	
20 "	0.3 c.c.	"	
25 "	0.35 c.c.	"	
27 "	0.4 c.c.	"	Given 0.15 c.c. 1:10,000 RAGWEED { Equal Parts
June			
			Given 0.3 c.c. "
1 "	0.5 c.c.	"	" 0.45 c.c. "
3 "	0.6 c.c.	"	" 0.6 c.c. "
6 "	0.7 c.c.	"	" 0.8 c.c. "
8 "	0.8 c.c.	"	" 0.95 c.c. "
10 "	0.9 c.c.	"	" 0.1 c.c. 1:1000
13 "	0.9 c.c.	"	" 0.2 c.c. "
15 "	0.9 c.c.	"	" 0.35 c.c. "
17 "	0.9 c.c.	"	" 0.5 c.c. "
20 "	0.9 c.c.	"	" 0.6 c.c. "
22 "	0.9 c.c.	"	" 0.75 c.c. "
28 "	0.9 c.c.	"	" 0.9 c.c. "
Spring Treatment Discontinued. *33 Doses.*			
July			
1 "	0.1 c.c.	1:100	
3 "	0.15 c.c.	"	
6 "	0.2 c.c.	"	
8 "	0.3 c.c.	"	
15 "	0.4 c.c.	"	
22 "	0.5 c.c.	"	
27 "	0.7 c.c.	"	
29 "	0.9 c.c.	"	
August			
1 "	0.1 c.c.	1:10	
3 "	0.15 c.c.	"	
5 "	0.2 c.c.	"	
8 "	0.3 c.c.	"	
10 "	0.4 c.c.	"	
12 "	0.5 c.c.	"	
15 "	0.6 c.c.	"	
17 "	0.7 c.c.	"	
19 "	0.8 c.c.	"	
22 "	0.9 c.c.	"	
24 "	0.9 c.c.	"	
26 "	0.9 c.c.	"	
31 "	0.9 c.c.	"	
September			
2 "	0.9 c.c.	"	
5 "	0.9 c.c.	"	
7 "	0.9 c.c.	"	
9 "	0.9 c.c.	"	
Summer Treatment Discontinued. *38 Doses.*			

Note:

1 c.c. Conc.	Timothy	= 0.5	mg. N.
1 c.c. 1:10	"	= 0.05	" "
1 c.c. 1:100	"	= 0.005	" "
1 c.c. 1:1,000	"	= 0.0005	" "
1 c.c. 1:10,000	"	= 0.00005	" "
1 c.c. Conc.	Ragweed	= 0.6	mg. N.
1 c.c. 1:10	"	= 0.06	" "
1 c.c. 1:100	"	= 0.006	" "
1 c.c. 1:1,000	"	= 0.0006	" "
1 c.c. 1:10,000	"	= 0.00006	" "

one must do so with conservative judgment, i.e., one may assume that in a given year without prophylactic treatment these patients would have suffered the amount of discomfort stated in their histories to have occurred in previous years.

Table II shows the results obtained by treatment of 116 patients in 1927. Had this group failed to take treatment, based on their statements as to symptoms in former years, the assumed number of days of disability would equal 5,256, an average of 45.3 days per person. This figure is reached after careful study of each history as given by the patient before treatment was commenced. Without treatment the spring and summer groups each averaged forty-two days, and the multiple pollen sensitive group (grass and ragweed sensitive patients) averaged seventy days of discomfort during the year. The study of the cards after the completion of treatment shows that in 1927 the group experienced 527 days of mild symptoms(two hours or less daily) and 663 days of severe symptoms (continuous during twenty-four hours), an average of 9.8 mild and severe days per person. There is a gain of 35.5 symptom-free days per person, or 78 per cent, as a result of the treatment.

TABLE II

SYMPTOMATIC COMPARISON OF A GROUP OF CASES WITHOUT TREATMENT AND THE SAME GROUP WITH TREATMENT IN THE YEAR 1927
NUMBER OF CASES REPORTED—116

WITHOUT TREATMENT	WITH TREATMENT	
Number of days of probable symptoms Mild and severe	Number of days of symptoms actually experienced by this same group Mild symptoms	Severe symptoms
5256 Days	527 Days	663 Days
Average number of days per person	Average number of days per person Mild symptoms	Severe symptoms
45.3 Days	4.5 Days	5.3 Days
	Total—9.8 Days	

45.3 Days of symptoms without treatment
9.8 Days of symptoms with treatment

35.5 Days less as a result of treatment, or a reduction as a result of treatment of 78%.

Table III shows the results obtained by treatment of ninety-three patients in 1928. The assumed number of days of discomfort was estimated at 4,382 or an average of 47.1 days. This group experienced 1,045 days of mild symptoms and 750 days of severe symptoms, an average of 19.2 days per person. There is a gain of 27.9 symptom-free days per person or 59 per cent as a result of treatment. It is to be remembered that this was a year of maximum pollen saturation and severe symptoms.

In 1929 one hundred and fifty patients showed results of treatment as tabulated in Table IV. The assumed number of days of discom-

fort was estimated at 6,944. This group experienced 1,270 days of mild symptoms and 914 days of severe symptoms, an average of 14.4 days per person. There is a reduction of 31.7 days per person or 68 per cent as a result of treatment.

TABLE III

SYMPTOMATIC COMPARISON OF A GROUP OF CASES WITHOUT TREATMENT AND THE SAME GROUP WITH TREATMENT IN THE YEAR 1928

NUMBER OF CASES REPORTED—93

WITHOUT TREATMENT	WITH TREATMENT	
Number of days of probable symptoms Mild and severe	Number of days of symptoms actually experienced by this same group Mild symptoms	Severe symptoms
4382 Days	1045 Days	750 Days
Average number of days per person	Average number of days per person Mild symptoms	Severe symptoms
47.1 Days	11.2 Days	8 Days
	Total 19.2 Days	

47.1 Days of symptoms without treatment
19.2 Days of symptoms with treatment

27.9 Days less as a result of treatment, or a reduction as a result of treatment of 59.2%.

TABLE IV

SYMPTOMATIC COMPARISON OF A GROUP OF CASES WITHOUT TREATMENT AND THE SAME GROUP WITH TREATMENT IN THE YEAR 1929

NUMBER OF CASES REPORTED—150

WITHOUT TREATMENT	WITH TREATMENT	
Number of days of probable symptoms Mild and severe	Number of days of symptoms actually experienced by this same group Mild Symptoms	Severe symptoms
6944 Days	1270 Days	914 Days
Average number of days per person	Average number of days per person Mild Symptoms	Severe symptoms
46.2 Days	8.4 Days	6.0 Days
	Total 14.4 Days	

46.2 Days of symptoms without treatment
14.5 Days of symptoms with treatment

31.7 Days less as a result of treatment, or a reduction as a result of treatment of 68%

Analysis of the group of patients with regard to specific pollen sensitivity is of interest. In the year 1929, for example, 150 patients were followed. Of this number thirty-seven had symptoms from grass pollen, twenty-three from both grass and ragweed pollen and ninety from ragweed pollen alone. In Table V the probable number of days of symptoms of each type is compared with the actual number of days of symptoms which the patients actually experienced. Of the three, the mixed group seems to have derived the greatest relief, although the variation of the three lies within 11 per cent.

TABLE V

COMPARISON OF THREE SEASONAL TYPES OF POLLEN-SENSITIVE PATIENTS (1929)

GROUP I. PATIENTS SENSITIVE TO GRASS POLLENS

NUMBER OF CASES—37

Without Treatment		*With Treatment*	
Average number of days of probable symptoms		Average number of days of symptoms actually experienced by this group per person	
Mild and severe per person	42 Days	Mild symptoms and severe symptoms	13 Days

42 Days of symptoms without treatment.
13 Days of symptoms with treatment.

29 Days of symptoms less as a result of treatment, or a reduction of 69%.

GROUP II. PATIENTS SENSITIVE TO GRASSES AND WEEDS

NUMBER OF CASES—23

Without Treatment		*With Treatment*	
Average number of days of probable symptoms		Average number of days of symptoms actually experienced by this group per person	
Mild and severe per person	70 Days	Mild symptoms and severe symptoms	18.6 Days

70.0 Days of symptoms without treatment.
18.6 Days of symptoms with treatment.

51.4 days of symptoms less as a result of treatment, or a reduction of 77%.

GROUP III. PATIENTS SENSITIVE TO RAGWEED

NUMBER OF CASES—90

Without Treatment		*With Treatment*	
Average number of days of probable symptoms		Average number of days of symptoms actually experienced by this group per person	
Mild and severe per person	42 Days	Mild symptoms and severe symptoms	14.1 Days

42.0 Days of symptoms without treatment.
14.1 Days of symptoms with treatment.

27.9 Days of symptoms less as a result of treatment, or a reduction of 66%.

That the treatment has been of great economic benefit is obvious. No one suffering with hay fever or asthma can work with maximum efficiency. In Table VI is presented a comparison of the data of this paper with the figures provided in a recent publication of Brundage[10] of the United States Public Health Service, on disability from respiratory disease. It must be noted that Brundage's figures represent actual days of disability, while the figures in this report refer to days of discomfort. In the same report Brundage gives a very clear comparison of the seasonal nature of respiratory diseases. It is well known that these diseases have a rise and fall depending on the winter and early spring months, and furthermore have certain characteristics suggesting hypersensitiveness to bacteria. Hay fever and

pollen asthma can, therefore, be compared on a similar basis with coryza, bronchitis or any of the mentioned diseases. Brundage's charts show that the peak of the occurrence of all respiratory diseases is maximum in February, the rise of which begins slowly in October, accelerates rapidly in December, and recedes with equal rapidity during March and April. The occurrence of pollen asthma and hay fever has three peaks, the first of which occurs in late April due to tree pollens, the second somewhat higher peak which occurs in June due to the grass pollens and the third extremely high peak which occurs in late August and early September due to the ragweed pollens.

TABLE VI

RESPIRATORY DISEASES CAUSING ABSENCE FROM WORK FOR ONE DAY OR LONGER AMONG EMPLOYEES OF THE EDISON ELECTRIC ILLUMINATING CO. OF BOSTON

	CALENDAR DAYS OF DISABILITY PER PERSON—ABSENCE
Sickness—exclusive of accidents	6.28
Respiratory diseases	5.66
Diseases of the nasal fossae and their adnexa	3.27
Bronchitis—acute and chronic	16.51
Diseases of the larynx	4.60
Diseases of the pharynx and tonsils	5.38
Influenza and grippe	12.87
Tuberculosis of the respiratory system	162.74
Pneumonia, all forms	43.99
Pleurisy	7.03

HAY FEVER AND POLLEN ASTHMA CAUSING DISCOMFORT (NOT ABSENCE FROM WORK) FOR TWO DAYS OR LONGER

Hay fever 1927 (untreated)	45.3
Hay fever 1928 (untreated)	47.1
Hay fever 1929 (untreated)	46.2

HERMAN AND DOULL'S GROUP OF 160 VOLUNTEERS "COLDS" AMONG JOHNS HOPKINS STUDENTS			ASSUMED DAYS OF DISCOMFORT—HAY FEVER GROUP
AVERAGE DURATION	AVERAGE NUMBER PER YEAR	TOTAL DAYS OF DISCOMFORT	
12.5 days	3.6 days	45 days	42 to 70 days

As is well known the seasons of hay fever and the common cold differ. It is definitely established, however, that discomfort from the common cold is of shorter duration than is discomfort experienced by an individual sensitive to pollen. Among 160 volunteers Herman and Doull* found that each averaged 3.6 "colds" during the year October 1, 1928, to September 30, 1929, and that the average duration of each cold (to termination of all symptoms) was approximately 12.5 days, a total of 45 days of cold during the year. It is assumed that a pollen sensitive individual without treatment will average from 42 to 70 days of symptoms, depending on the varieties

*Personal communication.

of pollen to which he is sensitive. However, it is not to be understood that in so far as life is concerned, hay fever is as dangerous as a common cold. The acute complications of the latter condition are well known. On the other hand asthmatic manifestations occur as a result of hay fever in many instances, gradually become perennial and finally the life of the individual terminates in acute myocardial failure, the indirect result of hay fever and asthma.

It seems fair to study the morbidity rate per thousand days with regard to pollen sensitive patients in much the same manner as one studies other respiratory disease morbidity. In Table VII is found comparison of the three years during which these patients were under observation. For example in 1927 assuming that one hundred and sixteen patients had failed to take treatment, their days of exposure were 42,340 and their assumed days of discomfort were 5,256. On the basis of 1,000 person days, therefore, the average disability per person per 1,000 days would be 124 days or discomfort 12.4 per cent of time. This same group, however, having received treatment had the same number of days of exposure but only 1,190 days of discomfort, and the morbidity rate per 1,000 person days was 28, or discomfort for 2.8 per cent of their time.

Making similar comparisons, in 1928 the morbidity rate per 1,000 person days in the group with no treatment was presumably 123 or 12.3 per cent of time; with treatment the discomfort was reduced to 52 days or 5.2 per cent.

TABLE VII

MORBIDITY PER 1000

	NUMBER OF PATIENTS A	DAYS OF EXPOSURE B	TOTAL DAYS OF DISABILITY C	MORBIDITY DISCOMFORT RATE PER 1000 PERSON DAYS
		(116 × 365 days)		$\left(\frac{C \times 1000}{B}\right)$
1927				
Hay Fever Patients (No Treatment)	116	42,340	5,256	124
Hay Fever Patients (With Treatment)	116	42,340	1,190	28
		(93 × 365 days)		$\left(\frac{C \times 1000}{B}\right)$
1928				
Hay Fever Patients (No Treatment)	93	33,945	4,382	123
Hay Fever Patients (With Treatment)	93	33,945	1,795	52
		(150 × 365 days)		$\left(\frac{C \times 1000}{B}\right)$
1929				
Hay Fever Patients (No Treatment)	150	54,750	6,944	126
Hay Fever Patients (With Treatment)	150	54,750	2,184	39

In 1929 the result of treatment was even better. Instead of losing 126 days per 1,000 days, by taking treatment the morbidity rate was reduced to 39 days of discomfort or 3.9 per cent of their time.

When one balances the economic gain obtainable from the treatment of pollen hay fever and pollen asthma against the practical failure of all forms of treatment shortening the course of respiratory diseases of the infectious type, it seems to me that more attention should be given to the former group of symptoms by those interested in public health problems. Unlike the symptoms of pollen-sensitive patients, the symptoms of acute respiratory diseases are self-limited. There is no specific treatment. Medical advisers of insurance companies fail to recognize the subsequent damage in a large percentage of untreated pollen asthmatics and pollen hay fever subjects. Public schools pay little attention to the asthmatic child or to a child with pollen hay fever, although on the other hand great effort is made to immunize the child against diphtheria; and the removal of infected adenoids and tonsils is urged when such foci are discovered. Because of the distressing disability which results from pollen hay fever, would it not be helpful if more attention were given to this problem in public schools and by students of public health, before the child becomes a subject of perennial asthma with secondary upper respiratory infection.

Though pollen hay fever and pollen asthma do not affect every member of the population, as does the common cold, there are estimated to be approximately 2,500,000 sufferers with these two conditions in the United States. The figures here presented as to the economic gain to patients obtainable from modern treatment methods may be balanced against the practical failure of all forms of treatment in shortening the course of acute infectious upper respiratory diseases.

This paper, therefore, is published to arouse a greater interest in individuals abnormally sensitive to pollen. Specific treatment decreases the incapacity. Students of life insurance, who are interested always in the "span of life," pass by this large group of sufferers without much consideration of the course of the disease. It is hoped that the time is not far off when hay fever and asthma will be given more thorough study by students of preventive medicine and will occupy a position comparable to the acute respiratory diseases and their sequelae.

SUMMARY

1. A chart and code for the recording of hay fever symptoms during the pollen season is suggested.

2. The method of treatment of pollen-sensitive patients as used in the clinic of the Johns Hopkins Hospital is outlined.

3. The results of treatment carried out over a period of three years, 1927, 1928 and 1929, are reported. The results are presented on a com-

parative basis, assuming that the individual patients would have a given number of uncomfortable days if prophylactic treatment had not been given. In 1927 as a result of treatment 116 patients averaged 9.8 days of mild and severe symptoms; in 1928, 93 patients averaged 19.2 days; and in 1929, 150 patients averaged 14.4 days.

4. Morbidity tables are presented showing the discomfort experienced per thousand person days.

REFERENCES

1. Walker, I. C.: Frequent Causes and Treatment of Seasonal Hay-fever, Arch. Int. Med. **28:** 71, 1921.
2. Cooke, R. A., and Vander Veer, A.: Human Sensitization, J. Immunol. **1:** 236, 1916.
3. Caulfield, A. H. W.: Desensitization of Hay-fever Patients by Injection and Local Application, J. A. M. A. **79:** 125, 1922.
4. Vander Veer, A.: The Present Status of the Treatment of Hay-fever and Asthma, Am. J. M. Sc. **164:** 97, 1922.
5. Rackemann, F. M.: The Results of the Specific Treatment of Late Hay Fever, J. Immunol. **11:** 81, 1926.
6. Ramirez, Maximilian, A.: Statistical Report on the Treatment of Hay-fever, Am. J. M. Sc. **176:** 856, 1928.
7. Piness, G.: Study of Two Hundred and Two Cases of Hay-fever, J. A. M. A. **84:** 584, 1925.
8. Coca, A. F.: Studies in Specific Hypersensitiveness, J. Immunol. **12:** 163, 1921.
9. Gay, L. N.: The Significance of Local Reaction in the Skin Following Deep and Superficial Injections of Pollen Extracts, J. ALLERGY **1:** 403, 1930.
10. Brundage, K.: Importance of Respiratory Diseases as a Cause of Disability Among Industrial Workers, U. S. P. H. Rep. **43:** 603, 1928.

THE DISTRIBUTION OF REAGINS IN THE BLOOD PLASMA*†

E. L. Sherrer, M.D.
Cleveland, O.

SINCE the demonstration of the presence of reagins in the blood of hypersensitive persons with positive skin tests, much work has been done on the specificity of reagins and the quantitative amounts of these substances in the blood. In 1925, Coca and Grove[1] studied extensively the specific relations between atopic antibodies and the specific antigens. They also investigated the neutralization effect of antigen reagin mixtures, both in vitro and in passive transfer sites. In 1926, Levine and Coca[2] worked out various methods for the quantitative estimation of reagins in serums. They demonstrated that the reagin content of serum changed very little during the desensitization of the allergic person. For the most part the technic of passive transfer has been used as a diagnostic method as suggested by Walzer,[3] or as a means of identifying and studying the atopic antigens.

As far as can be learned, no investigation of the distribution of reagins in the various fractions of the blood plasma has been undertaken up to the present time, nor has any attempt been made to isolate or concentrate these substances. Such a study was undertaken by us, therefore, not only on account of the interest in the chemistry of reagins as such, but also as a possible approach to the understanding of the general problem of hypersensitivity.

The separation of blood plasma into various fractions for the study of their immune body content has been done repeatedly. Banzhaf[4] employed this method for the investigation of the immune body in diphtheria antitoxin, and Avery[5] did similar work in the separation of pneumococcus antibodies from the whole serum. The chief groups of substances in the plasma are the diffusible crystalloids, the globulins, and the albumins. The globulins can be further divided into several fractions. Whether these fractions are entirely different protein is a matter of controversy. For present study the several globulins have been studied as distinct entities.

METHOD

Plasma and serum were obtained from hypersensitive persons with positive skin reactions. The serum was separated into various fractions by dialysis in order to obtain the diffusible portion and by precipitation with various salts in order to obtain the several protein

*Read before the Ninth Annual Meeting of the Association for the Study of Allergy, Philadelphia, June 8, 1931.
†From the Cleveland Clinic.

fractions. The euglobulin, pseudoglobulin I, pseudoglobulin II, and the albumins were precipitated by 33 per cent, 42 per cent, 50 per cent, and 100 per cent saturation of ammonium sulphate, respectively. The first three were separated also by 13.5 per cent, 17.5 per cent and 21.5 per cent concentration of sodium sulphate, according to the method of Howe.[6] After precipitation the protein was separated by high speed centrifugalization and then resuspended in normal salt solution. The concentration of the separated protein solution was made to equal the concentration of the same protein in the whole serum. The solutions were then tested by passive transfer for the presence of reagins and the relative amount contained in each solution. The method of dilution of the sensitizing solution was used. The antigen concentration remained constant throughout each experiment. Skin sites in normal individuals were sensitized by the injection of 0.1 c.c. of increasing dilutions of the sensitizing substance. Twenty-four hours later 0.03 c.c. of antigen solution was injected into each of the skin sites. The highest dilution which gave a positive reaction was used as a measure of the relative amount of reagin present in the sensitizing medium. Serum containing reagins for various substances, such as timothy, ragweed, egg white, were used.

DATA

By repeated experiments the plasma and serum were tested to determine which contained more reagin, and in each instance the relative amount of reagin present appeared to be equal. The total globulin was also tested against the whole serum to determine whether the entire quantity of sensitizing substance was carried in the globulin. The question also arose as to the possibility of the total globulins showing a higher concentration of reagins than the serum, just as the separated immune bodies for diphtheria and pneumococci are more potent than the whole immune serum, due to the presence of an inhibiting body in the serum. However, in each instance the whole serum was slightly more potent than the globulins.

The results of several experiments are tabulated in the following tables.

TABLE I

RAGWEED REAGINS—RAGWEED ANTIGEN 1:1000

SENSITIZING SUBSTANCE	DILUTIONS										
	1:2	1:5	1:10	1:20	1:30	1:40	1:50	1:60	1:70	1:80	1:100
Plasma	+	+	+	+	+	+	+	+	+	+	–
Serum	+	+	+	+	+	+	+	+	+	+	–
Serum dialysate	–	–	–	–	–	–	–	–	–	–	–
Euglobulin	+	+	–	–	–	–	–				
Pseudoglobulin I	+	+	+	+	–	–	–				
Pseudoglobulin II	+	+	+	+	+	+	–				
Albumins	–	–	–	–	–	–	–				

TABLE II

EGG WHITE REAGINS—EGG WHITE ANTIGEN 1:100

SENSITIZING SUBSTANCE	DILUTIONS							
	1:2	1:4	1:8	1:12	1:16	1:20	1:24	1:28
Plasma	+	+	+	+	+	+	+	–
Serum	+	+	+	+	+	+	+	–
Serum dialysate	–	–	–	–				
Euglobulin	+	+	–	–				
Pseudoglobulin I	+	+	+	–	–			
Pseudoglobulin II	+	+	+	+	+			
Albumins	–	–	–	–	–			

TABLE III

TIMOTHY REAGINS—TIMOTHY ANTIGEN 1:1000

SENSITIZING SUBSTANCE	DILUTIONS								
	1:2	1:5	1:10	1:20	1:30	1:40	1:50	1:60	1:80
Plasma	+	+	+	+	+	+	+	+	–
Serum	+	+	+	+	+	+	+	+	–
Serum dialysate	–	–	–	–	–	–			
Euglobulin	+	+	–	–	–	–	–		
Pseudoglobulin I	+	+	+	+	+	–	–		
Pseudoglobulin II	+	+	+	+	+	+	–		
Albumins	–	–	–	–	–	–			

TABLE IV

CHICKEN FEATHER REAGINS—CHICKEN FEATHER ANTIGEN 0.01 MG. N.

SENSITIZING SUBSTANCE	DILUTIONS						
	1:2	1:4	1:8	1:12	1:16	1:20	1:24
Plasma	+	+	+	+	+	+	–
Serum	+	+	+	+	+	+	–
Serum dialysate	–	–	–	–	–	–	
Euglobulin	+	+	–	–	–	–	
Pseudoglobulin I	+	+	+	–	–	–	
Pseudoglobulin II	+	+	+	+	–	–	
Albumins	–	–	–	–	–	–	

SUMMARY OF RESULTS

As stated previously, the plasma and serum are parallel in their reagin content. Apparently, the fibrinogen of the plasma does not increase the reagin concentration. The serum dialysate and the albumin fraction contained no trace of reagins. The globulins, particularly pseudoglobulin I and pseudoglobulin II, carried all of the sensitizing substance. The euglobulins in all cases gave evidence of comparatively small amounts of reagins. In each instance the pseudoglobulin II was slightly more potent than the pseudoglobulin I. In normal persons the average serum content of euglobulin is 0.5 per cent; of pseudoglobulin I, 1.1 per cent; of pseudoglobulin II, 1.6 per cent. It appears, therefore, that roughly, the reagin content of each fraction is proportional to the quantity of protein precipitated in each fraction. Thus far no inhibiting substance to the reagin has been demonstrated in the serum.

DISCUSSION

Little definite information is known as to the exact chemistry of immune bodies, complement-fixing bodies, and precipitins. Whether they are proteins or nonprotein substances adsorbed in the globulins has not been finally determined. Avery states that most workers believe them to be proteins. This opinion is supported by the observation that the action of proteolytic enzymes on immune body solutions causes a parallel disappearance of protein and immune bodies; whether this is true of reagins remains for future investigation.

As far back as 1914 Avery showed that Type I pneumococcus antibodies were contained in the globulins, chiefly pseudoglobulin I. In 1924 Kendrick and Kahn[7] demonstrated that the substance which is responsible for the positive Wassermann reaction is associated with the euglobulin and pseudoglobulin I fractions. The precipitins as a class are also contained in the globulin portion of the serum. Apparently the reagins do not differ from other immune bodies in being identified with the serum globulins. The more exact nature of these sensitizing substances is being made the subject of further investigation.

CONCLUSIONS

1. Plasma and serum contain similar amounts of reagin.
2. The albumins and the diffusible portion of the serum contain no reagins.
3. The globulins, particularly the pseudoglobulins, contain all of the reagins.
4. No substance which might inhibit a positive skin reaction has been demonstrated in the serum.
5. The reagins are similar to immune bodies in their association with the globulin fraction.

REFERENCES

1. Grove, E. F., and Coca, A. F.: Studies in Hypersensitiveness; Study of Atopic Reagins, J. Immunol. **10:** 455, 1925.
2. Levine, P., and Coca, A. F.: Studies in Hypersensitiveness. 1. Quantitative Study of the Interaction of Atopic Reagins and Atopen, J. Immunol. **11:** 411, 1926; 2. A Quantitative Study of Atopic Reagins in Hay Fever; Relation of Skin Sensitivity to Reagin Content of Serum, J. Immunol. **11:** 435, 1926.
3. Walzer, M.: Studies in the Absorption of Undigested Proteins in Human Beings; Simple Direct Method of Studying Absorption of Undigested Protein, J. Immunol. **14:** 143, 1927.
4. Banzhaf, E. J.: The Distribution of the Immune Bodies Occurring in Types I, II, and III Antipneumococcus Serum, Proc. Soc. Exper. Biol. & Med. **22:** 329, 1925.
5. Avery, O. T.: The Distribution of the Immune Bodies Occurring in the Antipneumococcus Serum, J. Exper. Med. **21:** 133, 1925.
6. Howe, P. E.: Determination of Proteins in the Blood: a Micro Method, J. Biol. Chem. **49:** 109, 1921.
7. Kendrick, P. L., and Kahn, R. L.: Precipitation With Fractions of Syphilitic Serum and Arachnoid Fluid, J. Infect. Dis. **39:** 202, 1926.

(For discussion, see page 502.)

THE DROPPING OUT OF POLLEN SEASONS

(Relation of the Pollen Content of the Air to Hay Fever, Asthma, and Dermatitis of the Exposed Parts)

W. W. Duke, M.D.
Kansas City, Mo.

THE relationship between the pollen content of the air at certain seasons and the symptoms, hay fever and asthma, was established by Blackley[1] in 1873 and since then has been unanimously verified by a host of observers. The importance of pollen as a cause of certain types of dermatitis of the face and hands observed by Sutton[3] and by Hannah[2] in 1919 has also been repeatedly verified.

Given the fact that the symptoms hay fever, asthma, and dermatitis of the exposed parts are frequently caused by pollen, it becomes necessary to know the pollen content of the air each day in order to understand some of the peculiarities of the disease. On the surface, pollen disease appears inconsistent in its behavior. The fact is, however, that no disease known to medical science is more consistent in its behavior than hay fever, asthma, and dermatitis caused by pollen. The tissues which happen to be sensitive to pollen react invariably and apparently in the same way each time they come in contact with pollen in adequate dosage.

The pollen content of the air varies grossly in different localities and at different seasons. In addition to this, the quantity which reaches the patient in a given locality and during a given season varies grossly. For example, I found that when the pollen content of the outside air was 191 per unit of air, it varied indoors from 0 to 20, depending upon the degree to which the outside air was excluded. Consequently, a patient in a closed room is exposed to only a small fraction of the pollen encountered by a patient in the outside air.

Another factor is also grossly important. I observed on one occasion that the quantity of pollen deposited per 30 seconds on a one-half square inch surface of a greasy slide was 0.6 granules by still outside air. At the same time and place, the quantity deposited behind the propellor of an aeroplane revolving at less than half speed was 82 per 30 seconds and at full speed was 289. Evidently air in motion is a gross factor therefore, in the rate at which pollen is deposited on surfaces. For this reason, exposure to wind and air currents encountered on railroad and automobile trips is a gross factor in determining the rate at which pollen is deposited on the skin surfaces. Wind, however, does not affect the rate of deposit on internal structures such as the

nasal and respiratory mucous membrane. Here, depth and rapidity of respiration are the gross factors. In fact, the rate of deposit of pollen upon the nasal and bronchial mucous membranes on a given day must depend directly upon the depth and rapidity of respiration.

Taking all these factors into consideration, the severity of reaction displayed by patients suffering from pollen disease should be expected to vary enormously from year to year and from day to day and in different patients in different, though possibly neighboring, environments.

It is the purpose of this paper to report estimations of the pollen content of the outside air made at daily intervals for a period of four years. The estimations were made by counting the number of pollen granules deposited on a sticky slide (0.55 square inch surface) left in the outside air for periods of twenty-four hours each day.

A brief note might be permitted here concerning the significance of so-called pollen counts—that is, counts of the number of pollen granules deposited on a unit of surface per twenty-four hours. This method of estimating the pollen content of the air is not overly accurate—in fact, the limit of error is gross. In the first place, a high count frequently has no more or no less significance than the fact that the wind is blowing. In the second place, on a windy day, the count varies grossly depending upon the position in which the slides happen to lie. For a period of one month, I compared counts made from slides placed outside a window, on the roof of a tall building, on the roof in a tall narrow jar, and on the roof in a bucket. The counts varied grossly. Variation depended apparently upon wind velocity and wind direction. Pollen deposit might be compared, in a way, with the drifting of snow. The depth and position of snowdrifts depend on wind velocity, wind direction, and obstruction to air currents. Pollen deposit is obedient grossly to the same physical laws. I know of no way of making pollen estimations in the outside air which eliminates this source of error. Consequently, estimations of the pollen content of the outside air are not more than relatively accurate.

Another important circumstance becomes apparent after the making of pollen counts over prolonged periods of time, namely, the fact that the pollen content of the air in a given locality depends more upon the quantity of pollen picked up by wind over vast areas of ground than upon the pollen picked up in the immediate vicinity. In fact, the pollen content of the air on the ground 200 yards from a ragweed patch may not be grossly different from the pollen content of the air at the top of a tall building or in an aeroplane 3,000 feet above the ground. A pollen storm apparently may be compared to a dust storm in which the dust picked up from vast ground surfaces may obscure the sun

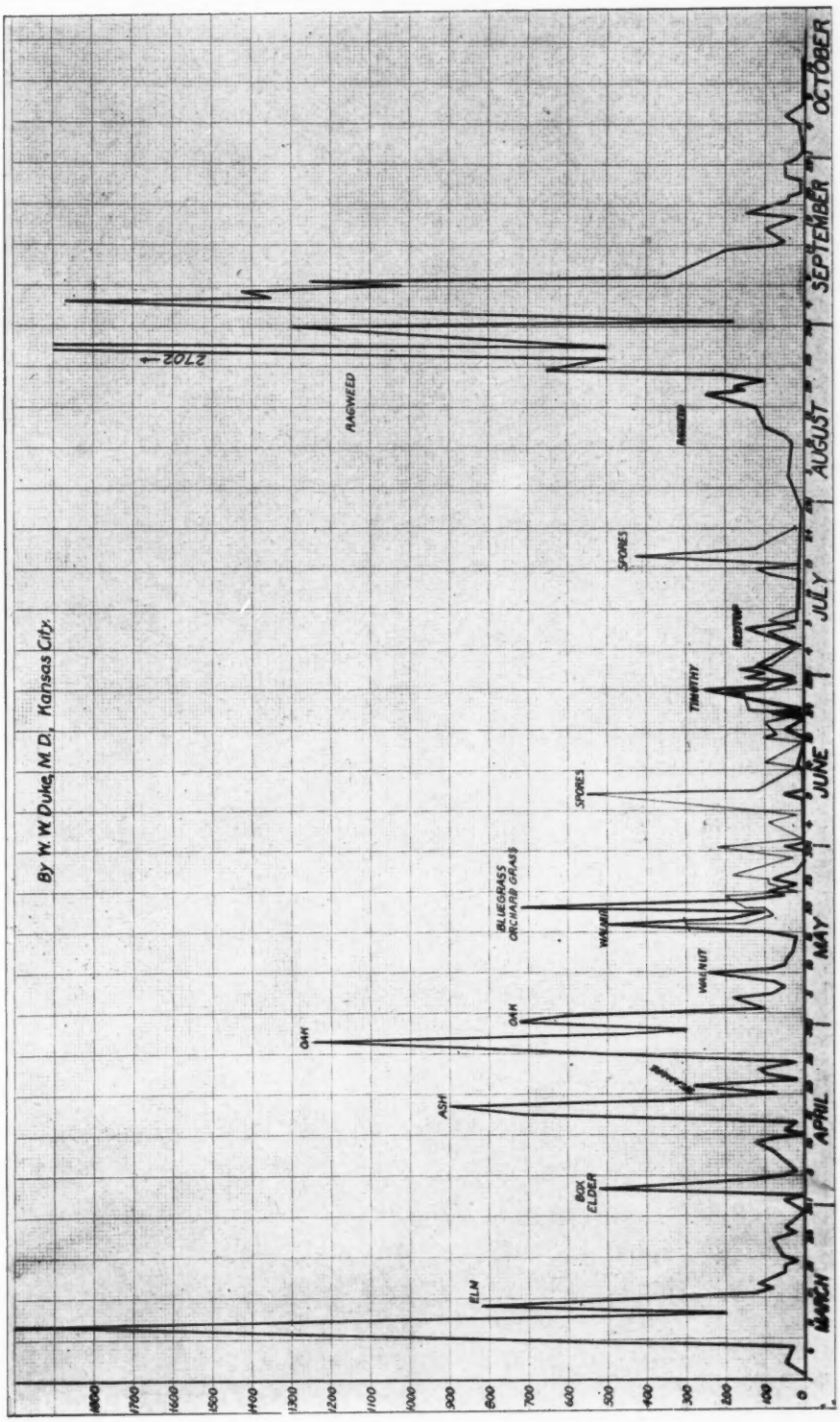


Chart 1.—Pollen chart for 1927.

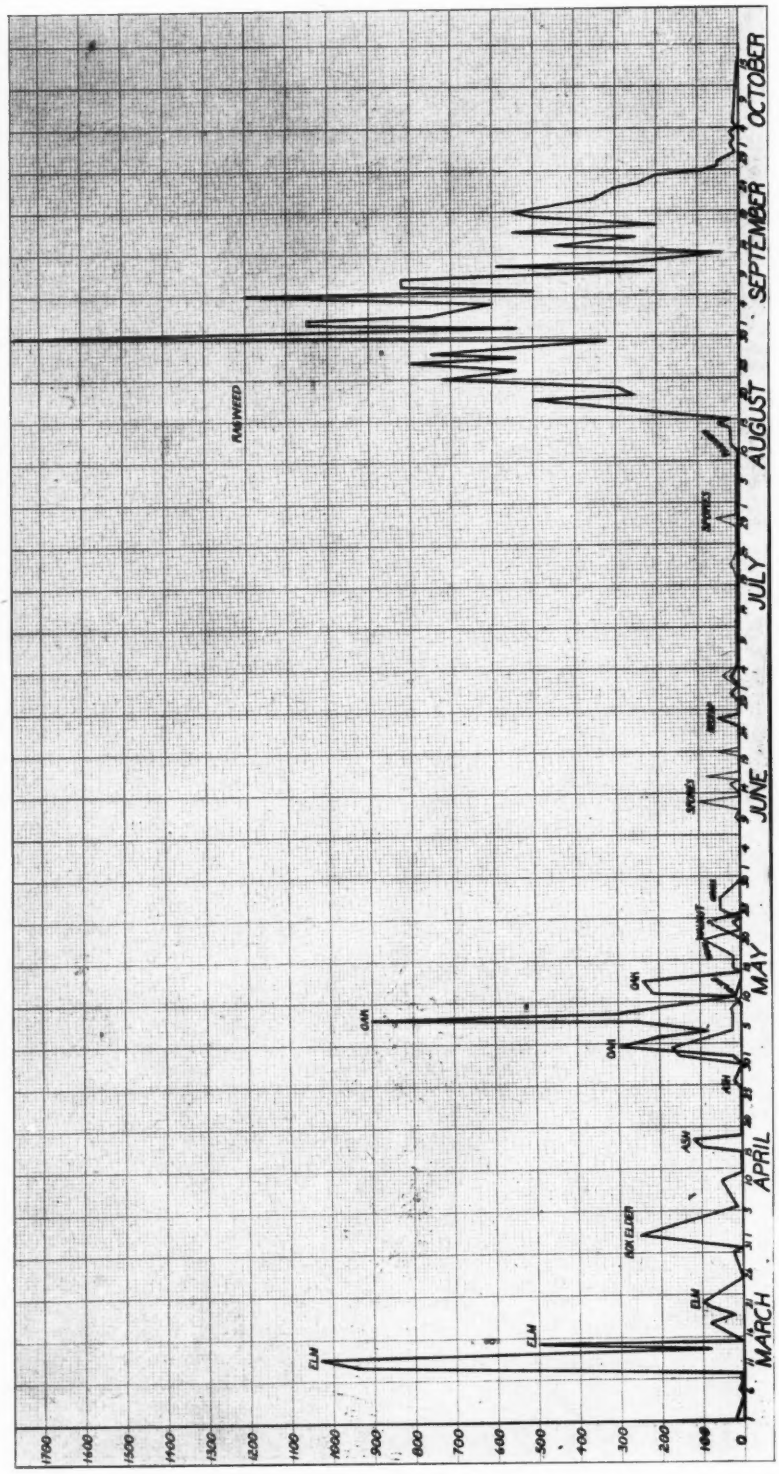


Chart 2.—Pollen chart for 1928.

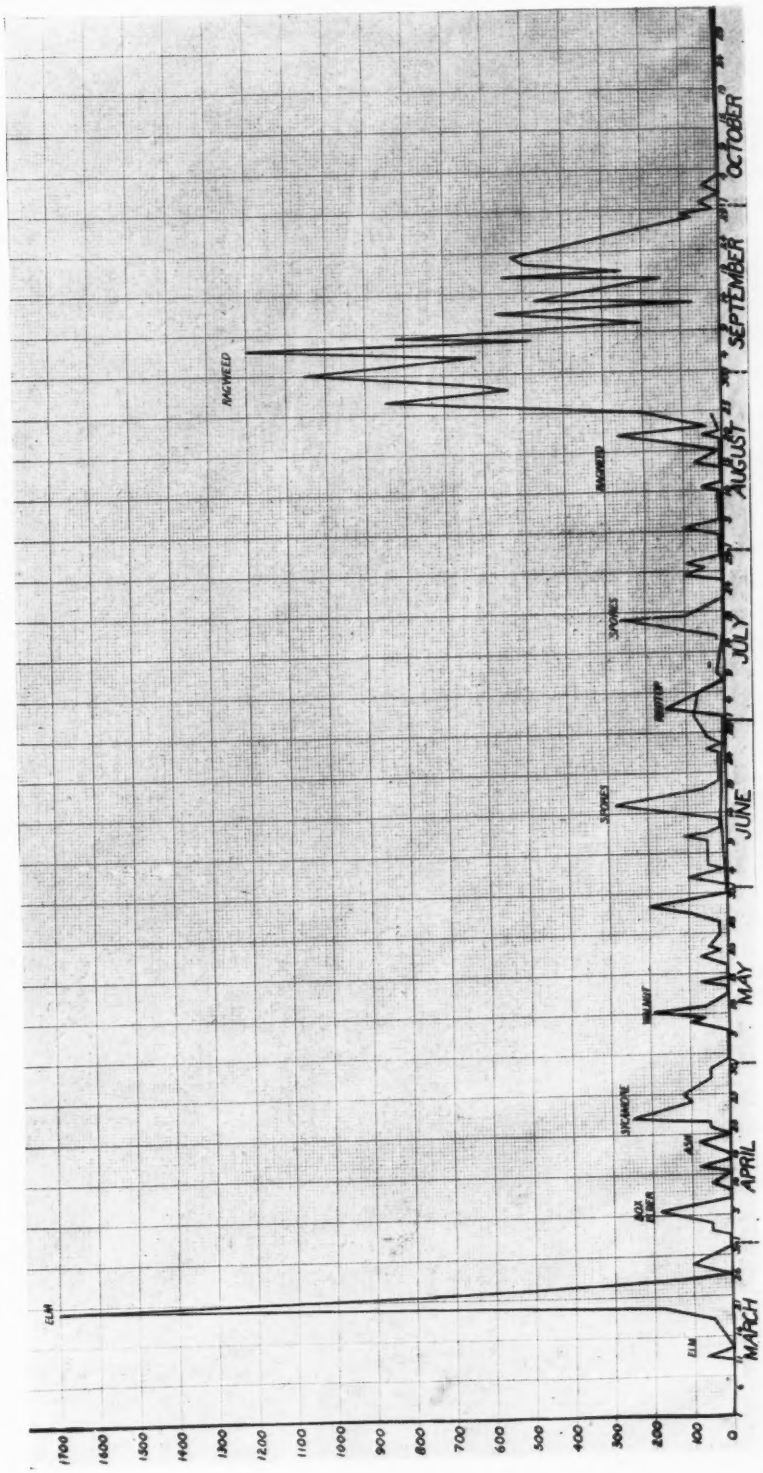


Chart 3—Pollen chart for 1929.

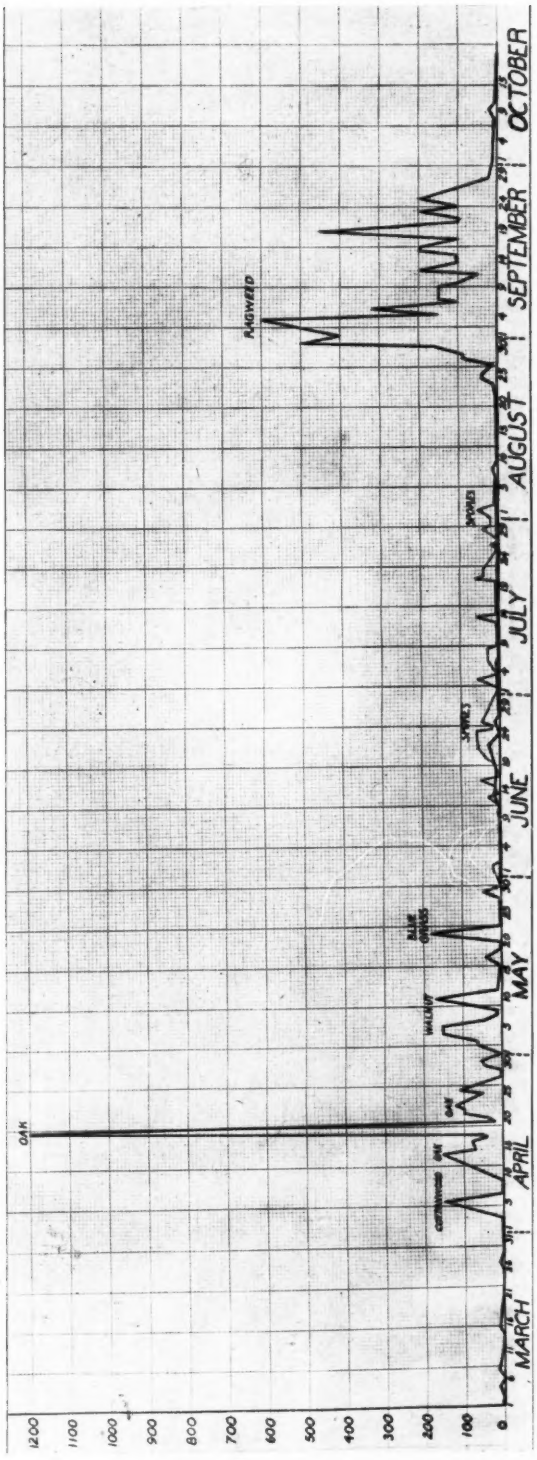


Chart 4.—Pollen chart for 1930.

and may not be grossly increased by the quantity picked up from nearby areas. Pollen is not grossly visible but apparently is carried about in much the same manner as dust.

Upon the charts reported below, it will be noted that in 1927, a normal season, the spring months are characterized by a number of huge so-called pollen peaks caused by the pollination first of elm, later of box elder, later of ash, sycamore, oak, and walnut. The spring season of succeeding years varies grossly from this—in fact, the normal season, 1927, is a very unusual season. The usual type of chart for the spring months are those shown for the years 1928, 1929, and 1930. The disappearance of one or more, or almost all the pollen peaks in the latter years were caused by spring frosts which cut short the pollination of the trees. The tree season in this district starts weeks before the budding of any of the trees, in fact, frequently in February when the ground is covered with snow. The early part of the season is due to pollen blown in from southern districts.

The summer season, the so-called grass season, is also subject to gross variance from year to year due almost entirely to rainfall or lack of rainfall. In 1927, the peaks shown in the latter part of May are due to blue grass and orchard grass and those in the latter part of June and early July are due to timothy and red top. These large peaks were almost completely missing in the subsequent three years due to drought which grossly affected the growth and pollination of the grasses. During the summer months, the air is at times filled with so-called spores, in fact, spore counts usually exceed grass pollen counts. The high spore counts noticed in 1927 were reduced to small factors in the subsequent three years.

Finally, the ragweed season, shown typically in 1927 with peaks occurring from the latter part of August to the middle of September, was markedly inhibited in 1928, still more in 1929, and was excessively reduced in 1930 by drought.

Within limits, one can predict what a given season will be. For example, with a luxuriant growth and blooming of the spring wild and hardy flowers and spring shrubbery, we can expect an intense tree season unless the pollination of a given tree happens to be cut short by frost. Climatic and soil conditions which favor spring blooming favor pollination of the trees.

With the prospects of a good wheat crop, we can expect a luxuriant grass season because of the fact that climatic and soil conditions which favor the wheat crop favor also the growth of the grasses.

Finally, with prospects of a bumper corn crop, we can expect an intense ragweed season. This, also, because of the fact that climatic and soil conditions which favor the corn crop favor also the growth and pollination of the fall weeds.

During the period of four years, it can be noticed that the pollen season for each tree, grass, and weed has been either reduced to a fraction of normal or reduced to a point of practical disappearance.

CONCLUSIONS

Estimations of the pollen content of the air made daily for a period of four years show that the normal season, 1927, in which all the trees, grasses, and weeds pollinated luxuriously, is a gross exception to the rule. Instead of the normal season, we usually find that the pollination of one or more or all of the trees or grasses or weeds is reduced grossly. This is caused in the spring season by frosts and in the summer and fall seasons chiefly by drought. During this period of four years, the pollination of each pollinating plant, except the ragweed, was almost completely inhibited once or for several seasons. The ragweed was not completely inhibited at any season but in 1930 was reduced to a small proportion of normal.

Pollen counts and pollen charts, such as these reported, are almost indispensable to the accurate diagnosis and treatment of pollen disease.

REFERENCES

1. Blackley, C. H.: Experimental Researches on the Causes and Nature of Catarrhus Aestivus (Hay Fever or Hay Asthma), London **7**: 202, 1873.
—: Hay Fever: Its Causes, Treatment and Effective Prevention, London, 2 Ed., 1880, Balliere, Tindall and Co.
2. Hannah, L.: Ragweed Dermatitis, J. A. M. A. **72**: 853, 1919.
3. Sutton, R. L.: Ragweed Dermatitis, Read before the Dermatological Section A. M. A., June, 1919, J. A. M. A. **73**: 1433, 1919.

STUDIES IN URTICARIA: THE INFLUENCE OF METABOLIC FACTORS*†

LEO H. CRIEP, M.D., AND LAWRENCE WECHSLER, M.D.
PITTSBURGH, PA.

URTICARIA is generally accepted to be a form of hypersensitiveness grouped with hay fever and bronchial asthma. Its causes are varied. Urticarial manifestations may occur as a result of direct contact with offending substances such as furs or wool, or with physical agents such as sunlight or heat; from the ingestion of certain foods, or from the administration of sera and drugs; and, lastly, as is believed by some, from sensitization to bacteria found in foci of infection. But regardless of etiology, the pathologic physiology is always the same; the wheal is produced as a result of the irritation of the skin and the skin capillaries with subsequent oozing and localized edema.

Because clinically it is not always possible to determine the allergic nature of a large proportion of urticaria cases, there have been numerous attempts made to find other factors influencing its development. This paper concerns itself, however, only with factors which may be grouped as metabolic; its purpose is to consider the available literature on the subject, and to report on a clinical and laboratory study of forty cases of urticaria with particular reference to the functional state of the gastrointestinal tract and the basal metabolism. A subsequent paper will report on other metabolic factors, such as the acid-base balance and blood chemistry.

TABLE I

AGE OF PATIENTS AND DURATION OF DISEASE

AGE	NO. PTS.	DURATION	NO. PTS.	DURATION	NO. PTS.
10-20 yr.	3	1 yr.	4	7 yr.	1
20-30 yr.	17	2 yr.	11	9 yr.	1
30-40 yr.	7	3 yr.	7	10 yr.	2
40-50 yr.	4	4 yr.	5	11 yr.	1
50-60 yr.	7	5 yr.	5	15 yr.	1
60-70 yr.	2	6 yr.	2		

The group of patients forming the basis for these observations is investigated first from the allergic viewpoint and presents the following findings: The distribution of the patients with regard to age and the duration of the disease may be seen in Table I. Positive intra-

†Read before the Ninth Annual Meeting of Association for the Study of Allergy, Philadelphia, June 8, 1931.

*From the Clinic of Applied Immunology, Medical School, University of Pittsburgh, and the Medical Service of the Montefiore Hospital, Pittsburgh, Pa.

dermal tests are obtained in practically all patients, but, in some, these reactions appear only as very doubtful. Only in nine patients, or 22 per cent, is a combined clinical and skin sensitivity found. Two patients, Cases 3 and 22, show allergy to physical agents such as heat and cold in addition to protein reactions. Ten patients have also other allergic manifestations such as eczema, hay fever, or asthma, and 14 give a positive history of familial allergy (Tables II and V).

TABLE II

ALLERGIC DATA ON FORTY CASES OF URTICARIA

	NO. PTS.	PER CENT
Intradermal skin tests positive	40	100
Proved clinical sensitivity	9	22
Physical allergy	2	5
Other allergic manifestations	10	25
Family history positive	14	35

I. THE GASTROINTESTINAL TRACT

Literature.—Acute, transient, urticaria is frequently relieved by the administration of a brisk saline purge. This accounts partly for the prevalent opinion that even in chronic urticaria disturbances in the function of the gastrointestinal tract and of the liver may be either direct or contributory etiologic factors. Thus, Eustis[1] reports that many urticaria patients have indican in the urine, and that this finding indicates absorption and subsequent detoxification by the liver of products of intestinal putrefaction. During the process of putrefaction the amino acids in the intestinal tract are converted into carbon dioxide and the corresponding amine, and one of these amines is histamine. Absorption of the latter may play an important rôle in urticaria, for, as Lewis shows,[2] in certain cases of physical allergy manifested by wheal formation, a histamine-like substance may be isolated from the skin; he believes that the liberation of this substance may have something to do with the production of the wheal. Bassler[3] also emphasizes the importance of paying closer attention to the gastrointestinal function in allergy, and states that abnormal intestinal absorption and biologic disturbances in the intestinal tract are important factors. Menagh[4] concludes from a study of 260 cases of angioneurotic edema and urticaria that in 48.8 per cent of his patients biliary tract disease is the only etiologic factor. Disease of the gall bladder and ducts in these patients leads to absorption of bacterial proteins, and in 73 per cent of his cases positive skin tests are obtained with cultures derived by biliary drainage. Furthermore, treatment directed toward the biliary tract and administration of vaccines from the bacteria isolated by drainage, resulted in the improvement of 88 per cent of the patients. Barber and Oriel[5] suggest that intimately associated with the allergic state is a condition of hepatic in-

sufficiency. They arrive at this conclusion from a study of the blood amino acids which they take as a good index of liver function. Their results show that the amino acids of the blood are increased during the acute urticarial attack indicating in this way some disturbance of hepatic function. Normally, the amino acids are absorbed from the intestines, reach the liver where they are deaminated, and finally find their way to the tissues. In conditions where extensive liver damage occurs, such as in acute yellow atrophy, deamination does not occur due to massive liver destruction and tissue autolysis. In these cases the amino acid of the blood is high. In conditions where the liver damage is not quite so extensive, such as in cirrhosis, no such finding occurs. Since there is no demonstrable liver lesion in urticaria, it is difficult to see why it should be associated with a high blood amino acid, and we believe that such a finding when present should not necessarily be interpreted as a sign of hepatic deficiency. Procedures available for the determination of liver function other than its bile forming ability, are at best not very useful. They are positive only after such extensive damage has occurred in the organ, that this damage is recognizable easily by clinical methods.

Findings.—In order to determine the presence of an organic or functional gastrointestinal disturbance in urticaria, 40 patients are studied. This study includes a careful history and physical examination, and, with the exception of only several instances, such laboratory investigations as gastric analysis, examination of feces, biliary drainage, icterus index, Van den Bergh, bromsulphthalein excretion, cholecystogram, and complete roentgen-ray study of the gastrointestinal tract. The results of this investigation are shown in Table III. Of the entire group only eight patients, or 20 per cent, are free from any evidence of digestive disturbance. The rest present various types of involvement. Thus, about one-third of the patients give a history of gastric upsets, constipation, and "indigestion." Twenty-one per cent have gastric hypoacidity and 23.7 per cent have achylia. On roentgen-ray study, 20 per cent show atony and ptosis, and 36.6 per cent show spasticity of the colon. Twenty patients, or 50 per cent of the group, show some laboratory or clinical evidence of gall bladder tract disease. It is true that in only a much smaller number of cases is there a picture of clear-cut and definite cholecystitis. In many cases there are only isolated positive laboratory tests suggesting gall bladder involvement, the findings being as follows: Ten of 34 patients, or 29 per cent, gave x-ray evidence of gall bladder disease; 13 of 25 patients, or 52 per cent, had an icterus index above seven indicating a slight degree of latent icterus, and three of 22 patients, or 13.6 per cent, had a positive Van den Bergh. Biliary drainage was done on 19 patients and the material was examined microscopically and cultured occasionally. In

12 patients, or 63 per cent, there is evidence of some infection in the gall bladder as shown by the finding of many pus cells in the bile. In 11 patients, or 57.8 per cent, there is some disturbance in the function of the gall bladder concerned with bile metabolism as evidenced by the presence of cholesterol crystals (Table III). None of the patients so tested show liver insufficiency as determined by the excretion of bromsulphthalein (Table V). One patient shows peptic ulcer; one, colon mucorrhea; three, chronic appendicitis; and three, manifestations of gastrointestinal allergy.

TABLE III

GASTROINTESTINAL DISTURBANCES IN URTICARIA

PTS. EXAM.	NATURE OF DISTURBANCE	NO. PTS.	PER CENT
40	Entirely free of any gastrointestinal or gall bladder disturbance	8	20
40	History of "indigestion," constipation, etc.	13	32.5
38	Gastric hypoacidity	8	21
38	Achylia	9	23.7
30	Atony and ptosis of stomach	6	20
30	Spastic and hypermotile colon	11	36.6
34	Gall bladder disease: X-ray positive	6	17.3
34	Gall bladder disease: X-ray suggestive	4	11.7
25	Gall bladder disease: Icterus index above 7	13	52
22	Gall bladder disease: Van den Bergh positive	3	13.6
19	Gall bladder disease: Biliary drainage: Infection	12	63
19	Gall bladder disease: Biliary drainage: Disturbance in pigment formation	11	57.8
40	Patients showing some evidence of gall bladder disturbance	20	50
40	Ulcer	1	2.5
40	Colon mucorrhea	1	2.5
40	Chronic appendicitis	3	7.5
40	Gastrointestinal allergy	3	7.5

COMMENT

A discussion of metabolism does not as a rule include consideration of gastrointestinal function, but for the purpose of the present paper it is taken up because it is so closely linked with other metabolic factors related to urticaria. Furthermore, analysis of the findings obtained in the examination of the gastrointestinal tract in this group indicates that the digestive tract is involved in a fairly large percentage of cases. This involvement is entirely too frequent to be purely coincidental and must bear some indirect but contributory share in the production of the urticarial state. It is true that there may be a functional involvement of the gastrointestinal tract in otherwise normal individuals but this fact would in no way affect the conclusions to be derived from such an involvement in urticaria patients. Whereas incomplete digestion and imperfect nitrogen metabolism usu-

ally may not give rise to any clinical manifestations, in urticaria such changes may affect the general state of susceptibility and produce symptoms. In an attempt to interpret the rather high incidence of achylia and hypoacidity in these cases, the possibility of senile atrophy of the gastric mucosa can be ruled out on account of the age of the patients in this series. A number of these individuals, however, have some associated biliary tract disturbance, and in this condition regurgitation of duodenal fluid is not uncommon. Furthermore, the presence of toxemia from foci of infection, the presence of congestion of the mucous membrane of the stomach, and nervous influences, particularly those of the sympathetic system, may play an important rôle in this connection. But regardless of its mechanism of production, a deficiency in gastric acidity may, according to Beckman,[6] disturb the acid-base balance of the individual and thus contribute to the allergic state. Changes in motility, such as atony and spasm lead to constipation and stasis, and this in turn may cause intestinal absorption either of toxic substances or of incomplete split-up products of protein digestion. Such substances may produce urticaria either as a result of their irritative nature, or because the shock organ, that is, the skin, is actually sensitive to them. Derangement in the condition of the gall bladder may also be a factor, either because of interference with the supply of normal bile, which would also affect digestion, or because of infection. Whether the gall bladder acts as a focus of infection and sensitizes the individual to bacterial proteins thus absorbed is a matter still open to question. The specificity of skin reactions to bacterial emulsions is not sufficiently established to render positive reactions obtained with vaccines prepared from biliary drainage material as entirely convincing.

A great deal would be contributed toward a better understanding of possible etiology and treatment of some of the more obscure cases of urticaria if it were possible to prove its association with hepatic insufficiency, particularly with impairment of that function of the liver which is concerned with nitrogen metabolism. Such knowledge may reveal imperfect nitrogen metabolism in the liver as the factor responsible for the occurrence of incompletely metabolized substances to which the patient is sensitive.

TABLE IV

BASAL METABOLIC RATE IN THIRTY-ONE CASES OF URTICARIA

	NO. PTS.	PER CENT
Total number of patients studied	31	
Normal minus 10 to plus 17	20	64.5
Increased thyroid activity	8	26
Decreased thyroid activity	3	9
Total number of disturbed thyroid	11	35

TABLE

THE RÔLE OF VARIOUS METABOLIC

NO.	AGE	WT.	ALLERGY				GASTROINTESTINAL		
							STOMACH AND		
			DURATION	SKIN TESTS	OTHER ALLERGY	F. H.	HISTORY	SIGNS	GASTRIC EXAM. HCL / T. A.
1	20	98	2	+	Asthma	Neg.	Constipation	None	Normal
2	28	134	3	+	None	+	Constipation	Tender G. B.	5 / 18
3	26	109	2	+	None	Neg.	Constipation	None	10 / 28
4	24	134	6	±	Ang. N. E.	+	Neg.	None	0 / 15
5	42	118	2	+	None	Neg.	Constipation	None	31 / 54
6	49	141	4	+	None	Neg.	None	None	0 / 21
7	28	124	5	+	Eczema	+	None	Tender G. B.	-- / --
8	35	122	2	±	None	Neg.	None	None	14 / 24
9	21	129	5	±	Ang. N. E.	+	Constipation	None	0-8 / 14
10	39	150	7	+	None	Neg.	None	None	12 / 29
11	21	115	4	+	None	+	None	None	14 / 31
12	24	142	4	±	Eczema	Neg.	None	None	Normal
13	29	129	2	+	None	+	None	None	Normal
14	19	114	1	+	None	+	None	None	Normal
15	25	120	1	+	None	Neg.	None	None	Normal
16	51	180	10	±	Ang. N. E.	Neg.	None	None	Normal
17	17	122	1	±	None	Neg.	None	None	Normal
18	31	96	5	±	None	+	None	None	0 / 0
19	64	180	3	±	None	Neg.	None	None	Normal
20	56	146	2	+	None	Neg.	None	None	Normal
21	54	130	9	+	None	Neg.	Constipation	None	0 / 6
22	29	125	5	++	None	+	Constipation	None	Normal
23	20	93	6	±	None	+	None	None	12 / 21
24	55	159	3	+	None	Neg.	None	None	0 / 10
25	36	143	2	+	None	Neg.	Indigestion	None	Normal
26	37	160	10	+	H. F.	+	None	None	12 / 25
27	22	165	2	±	None	Neg.	None	None	Normal
28	58	160	1½	±	None	Neg.	Nausea. Constipation	Tender G. B.	0 / 15
29	54	138	3	+	None	Neg.	None	None	Normal
30	62	130	3	+	None	Neg.	Diarrhea	None	Normal
31	42	160	4	+	None	Neg.	None	None	15 / 20
32	56	141	2	+	None	Neg.	Indigestion	Tender G. B.	0 / 20
33	32	131	15	+	None	Neg.	None	None	0-4 / 16
34	48	123	1½	+	Drugs	Neg.	None	None	Normal
35	33	118	5	±	None	Neg.	None	None	0 / 20
36	11	110	4	+	H. F.	+	None	None	4 / 22
37	29	91	11	±	Asthma	+	None	None	Normal
38	21	140	3	+	None	Neg.	Indigestion	None	0 / 32
39	24	120	3	±	H. F.	+	Constipation	None	Normal
40	23	124	2	+	None	Neg.	None	None	----

V

FACTORS IN URTICARIA

TRACT INTESTINES		GALL BLADDER							BASAL METABOLISM
X-RAY SERIES	FECES	X-RAY	BROMSULPHTHALEIN	ICT. INDEX	VAN DEN BERGH		BILIARY DRAIN		
					DIR.	IND.	INF.	PIGMENT	
Good tonus	Neg.	Faint shadow	0, less 15%	+5	Neg.	Neg.	+	+	+ 5
Ptosis and atony. Colon catarrh	Neg.	Faint shadow	0, less 15%	+8	Neg.	Neg.	+	+	+10
Normal	Neg.	Normal	0, less 15%	+9	Neg.	Neg.	+	+	+17
Ptosis. Spasmotic colon	Neg.	Normal	0, less 15%	+8	Neg.	Neg.	+	+	+19
Normal	Neg.	Normal	0, less 15%	+5	Neg.	Neg.	Neg.	Neg.	− 3
Poor tonus. Spastic colon	Neg.	Normal	0, less 15%	+7	Neg.	Neg.	+	+	− 4
Normal	Neg.	No shadow seen	0, less 15%	+5	Neg.	Neg.	Neg.	Neg.	− 5
Stasis in colon	Neg.	Normal	0, less 15%	+8	Neg.	Neg.	+	+	+25
Spastic pylorus	Neg.	Normal	0, less 15%	+6	Neg.	Neg.	Neg.	Neg.	+23
Spastic colon	Neg.	Normal	0, less 15%	+6	Neg.	Neg.	+	+	− 5
Poor tonus. Spastic colon	Neg.	Normal	0, less 15%	+8	Neg.	+1	+	+	+19
Normal	Neg.	Normal	0, less 15%	+9	Del. +	Neg.	Neg.	Neg.	+10
Fair tonus. Some stasis	Neg.	Normal	0, less 15%	+9	Del. +	+	Pos.	Neg.	+10
Normal	Neg.	Normal	0, less 15%	+6	Neg.	+	Neg.	Neg.	+ 3
Normal	Neg.	Normal	0, less 15%	+5	Neg.	+	Neg.	Neg.	−24
Normal	Neg.	Normal	0, less 15%	+9	Neg.	+	Neg.	Neg.	+17
Normal	Neg.	Normal	0, less 15%	+7	Neg.	+	--	--	+19
Atony of stomach. Hypermotility	Neg.	Normal	0, less 15%	+8	Neg.	+	--	--	+33
Normal	Neg.	Normal	0, less 15%	+5	Neg.	Neg.	--	--	+ 1
Gastric ulcer	Neg.	Normal	0, less 15%	--	--	--	--	--	--
Normal	Neg.	Normal	------	--	--	--	--	--	--
Hypermotility of colon	Neg.	Normal	------	--	--	--	--	--	--
Ptosis and dilatation colon	Neg.	Normal	------	--	--	--	--	--	+37
Normal	Neg.	Large shadow	------	+5	--	--	--	--	--
Pylorospasm	Neg.	------	------	--	--	--	+	+	--
Hypertonic	Neg.	------	------	--	--	--	--	--	− 9
------	Neg.	------	------	--	--	--	--	--	− 7
------	Neg.	Faint outline	------	+9	--	--	+	+	+12
------	Neg.	No shadow	------	+8	--	--	--	--	--
------	Neg.	------	------	--	--	--	--	--	--
Spastic colon	Neg.	------	------	--	--	--	--	--	--
------	Neg.	No shadow	------	--	--	--	+	+	--
Spastic colon. Stasis	Neg.	Normal	------	--	--	--	--	--	+ 4
------	Neg.	Normal	------	--	--	--	--	--	+13
------	Neg.	No shadow	------	+8	Neg.	Neg.	--	--	−11
Normal	Neg.	------	------	--	--	--	--	--	−26
------	Neg.	No shadow	------	+9	Neg.	Neg.	--	--	+16
------	Neg.	No shadow	------	+7	Neg.	Neg.	--	--	+21
------	Neg.	Normal	------	--	--	--	--	--	+20
Spastic colon	Neg.	Normal	------	--	--	--	--	--	+ 5

II. BASAL METABOLISM

Literature and Findings.—In a previous communication[7] we pointed out that there is some disturbance in the basal metabolic rate in various allergic conditions: Roussel[8] discusses such changes in chronic urticaria in the light of thyroid-adrenal dysfunction and indicates that it may be the cause of the vasomotor instability present in these individuals. The involuntary nervous system sends two nerve branches to the walls of the blood vessels. Stimulation of one branch leads to vasodilatation, stimulation of the other to vasoconstriction. Thyroid secretion stimulates the former and produces vasodilatation, while adrenalin stimulates the latter and produces vasoconstriction. Hence, a determination of the basal metabolism is of value, according to the above named writer, not only because it indicates which one of the conditions is present, but also because it may serve as a guide to treatment. Following is a report of basal metabolic determinations on 31 patients. The outer limits of the normal rate is considered ranging between minus 10 and plus 17 per cent. The highest reading in this group is plus 37 per cent. Three patients, or 9 per cent, show a condition suggesting lessened thyroid activity, the lowest basal metabolic rate being minus 24 per cent. It seems, therefore, that about 35 per cent of the patients studied in this group have some increase or decrease in basal metabolic rate. (Tables IV and V.) These determinations are made more than once on each patient and are carefully checked. Clinically, most of the patients show slight hyperthyroid or hypothyroid signs and symptoms, but all except one are to be considered borderline cases. This patient presents the clinical picture of hypothyroidism. The etiologic importance of such deviations from the normal must not be given too much significance for patients with thyroid dysfunction do not usually present urticaria as an associated condition, and conversely, only a small percentage of urticaria patients have thyroid imbalance. This imbalance may rather contribute to the general make-up of the patient, rendering him less stable and more susceptible to the exciting cause.

An analysis of the above findings leads one to the conclusion that changes in the gastrointestinal and thyroid function are for the most part either coexisting with, contributory to, or resulting from the urticarial state. They are not sufficiently specific to bear a direct causal relation to urticaria. They may increase an existing predisposition and contribute to the general state of susceptibility of the patient. Urticaria patients frequently give a positive familial allergic history. They frequently present manifestations of other allergic states. Their condition is traceable in a variable percentage of cases directly to contact with some specific substance. Hence the common denominator in these cases is hypersensitiveness.

REFERENCES

1. Eustis: Relation of Intestinal Toxemia to Allergy, South. M. J. **23**: 308, 1930.
2. Lewis, Thomas: The Blood Vessels of the Human Skin and Their Responses, 1927, Chicago Medical Book Co.
3. Bassler, Anthony: Intestinal Toxemia, New York, 1930, F. A. Davis.
4. Menagh, Frank R.: The Etiology and Results of Treatment in Angioneurotic Edema and Urticaria, J. A. M. A. **90**: 668, 1928.
5. Barber, W. H., and Oriel, H. G.: A Clinical and Biochemical Study of Allergy, Lancet **41**: 1009, 1928.
6. Beckman, Harry: Allergy and the Acid Base Balance, J. A. M. A. **95**: 1582, 1930.
7. Criep, Leo H., and McElroy, William S.: Blood Calcium and Gastric Analysis, Arch. Int. Med. **42**: 865, 1928.
8. Roussel, J. N.: Chronic Urticaria, Thyroadrenal Syndrome; How to Determine Direction of Dysfunction, and What Type of Agents to Employ in Treatment, South. M. J. **22**: 668, 1929.

1004 MAY BUILDING.

(For discussion, see page 507.)

BASAL METABOLISM AND BLOOD CALCIUM STUDIES IN ASTHMA AND ALLERGIC ECZEMA*†

RICHARD A. KERN, M.D., AND IDA TELLER, B.A.
PHILADELPHIA, PA.

PART I. BASAL METABOLISM STUDIES

THE data in the history of many allergic patients suggest a possible relation of an endocrine dysfunction to their allergic disease. Especially to the thyroid has an etiologic rôle been assigned by various writers, and thyroid therapy has received considerable attention in allergic conditions. However, the available clinical evidence is contradictory. For example, Widal and Abrami[1] reported a case of asthma with myxedema in which thyroid feeding cured the asthma. But they also cite three cases of Graves' disease with asthma in which the asthma improved and eventually cleared up parallel with the improvement in thyrotoxicosis.

Experimentally, there has been found some relation between the thyroid and anaphylaxis. Kepinow,[2] Houssay and Cisneros,[3] and Nechkovitch,[4] have found that thyroidectomy in dogs and rabbits greatly lessen and occasionally prevent anaphylactic shock. Popea and Constantinescu[5] injected horse serum into ten patients; four of them hypothyroid, one hyperthyroid and five without thyroid disease; 25 days later they injected blood of these patients into guinea pigs and then tried to produce anaphylactic shock in the animals by an injection of horse serum. Severe shock occurred in the animal that had received blood from the hyperthyroid patient, moderate shock in those injected with blood from the nonthyroid persons, and little or no shock in those who had received blood from the hypothyroid patients.

There have been few accurate or extensive clinical studies of the thyroid factor in allergic disease. In 1928 Criep and McElroy[6] reported metabolic rates in 17 allergic persons, only six of whom were asthmatic. Their figures were normal or slightly above normal. Novak[7] in 1921 reported one case of asthma with a normal metabolic rate and Simpson[8] in 1922 also found a normal metabolic rate in three asthmatic patients.

It therefore occurred to us to study the basal metabolisms of a considerable series of asthmatic patients to see if the findings would point

*From the Allergy Section of the Medical Clinic and the Metabolic Section of the Pepper Laboratory of Clinical Medicine of the Hospital of the University of Pennsylvania.

†Read before the Association for the Study of Allergy, Philadelphia, June 8, 1931.

TABLE I

BASAL METABOLIC RATES IN 75 ASTHMATICS

CASE NO.	B.M.R. %	SEX	GOITER	FAMILY HISTORY GOITER	ASTHMATIC SYMPTOMS ACTIVE OR INACTIVE
		Allergic Asthma			
1	−28	M	−	−	A
2	−24	F	+	0	I
3	−24	F	0	0	I
4	−23	M	0	0	A
5	−20	F	0	0	I
6	−15	F	+	−	I
7	−15	M	0	0	A
8	−14	F	?	−	A
9	−14	M	0	0	A
10	−14	M	0	0	A
11	−14	F	?	0	I
12	−13	F	0	0	A
13	−11	M	0	−	I
14	−11	F	0	0	A
15	−10	M	0	0	I
16	−10	F	?	0	I
17	− 9	F	0	0	I
18	− 9	F	+	+	A
19	− 8	M	0	0	A
20	− 8	M	0	0	I
21	− 7	F	0	0	A
22	− 7	F	0	0	A
23	− 6	F	+	+	I
24	− 6	F	0	0	I
25	− 4	M	0	0	I
26	− 2	M	0	0	I
27	− 2	M	0	0	A
28	− 2	F	+	0	A
29	+ 1	M	+	+	A
30	+ 1	M	+	0	A
31	+ 1	F	0	0	A
32	+ 1	M	0	0	I
33	+ 2	F	?	0	I
34	+ 2	M	0	0	I
35	+ 2	F	0	0	A
36	+ 2	F	0	0	A
37	+ 2	F	+	+	A
38	+ 3	M	0	−	A
39	+ 4	F	0	0	A
40	+ 4	F	0	0	A
41	+ 5	F	0	0	A
42	+ 5	F	+	0	I
43	+ 7	F	0	0	I
44	+ 7	F	−	−	A
45	+ 7	M	0	0	A
46	+ 7	F	0	0	A
47	+ 8	F	+	+	A
48	+ 8	F	0	0	I
49	+ 9	M	?	−	A
50	+ 9	M	0	0	A
51	+ 9	M	0	−	I
52	+10	M	0	−	I
53	+13	M	0	0	I
54	+18	M	0	0	A
55	+20	F	0	+	A

TABLE I—CONT'D

CASE NO.	B.M.R. %	SEX	GOITER	FAMILY HISTORY GOITER	ASTHMATIC SYMPTOMS ACTIVE OR INACTIVE
		Infectious Asthma			
56	−16	F	0	−	A
57	−14	F	−	−	I
58	−14	F	0	0	I
59	−12	F	0	0	I
60	− 9	F	+	0	I
61	− 7	M	0	−	I
62	− 7	M	0	0	A
63	− 6	M	0	0	A
64	− 4	F	+	0	I
65	− 2	F	0	−	I
66	− 1	M	0	−	A
67	− 1	F	+	0	A
68	± 0	F	0	0	A
69	+ 1	F	0	0	I
70	+ 2	F	0	0	A
71	+ 5	F	0	0	A
72	+ 5	M	0	0	I
73	+ 6	M	0	0	A
74	+10	M	+	0	A
75	+17	F	+	0	A

to any associated thyroid disturbance. Observations were made on 75 asthmatic patients seen in the Allergy Section of the Medical Clinic of the Hospital of the University of Pennsylvania. The patients ranged in age from fourteen to eighty-one years; there were 43 females and 32 males. In 55 patients the asthma was allergic in etiology, and in 20 it was infectious. All patients had had active symptoms in the few weeks preceding this study. In order to make the reading a truly basal one, all patients with any but very mild symptoms of asthma were not considered as suitable material and were studied at a later date when symptoms were minimal or absent.

In Table I are recorded the basal metabolic readings together with the available data of the presence or absence of thyroidal enlargement, of a family history of goiter, and a notation as to whether symptoms of asthma were active or inactive at the time of the test. Patients who had mild asthma at the time of the test, or who had had definite asthma within twelve hours preceding the test, were designated as active.

To facilitate the examination of the basal metabolism rates, we have summarized them in Table II.

If we accept plus 10 and minus 10 as the limits of normal, then it will be seen that the great majority of cases, 53 or 71 per cent, fall within this range. Only 4 patients had metabolic rates over plus 10, and in 3 of the 4, active symptoms had been present shortly before the test was made. One patient with an infectious asthma of fourteen years' duration had a goiter and moderate tachycardia but no other

evidence of thyrotoxicosis. She also had moderate asthma in the night preceding two metabolic rate studies, with readings of plus 25 and plus 17 respectively. The other 3 patients with elevated readings showed no further signs of thyroid hyperfunction. A significant number of readings in the allergic group fell below minus 10. Fourteen of the allergic group, 25 per cent, gave low readings. Four of the allergic group gave readings under minus 20, the actual figures being minus 23, minus 24, minus 24, and minus 28. Only 3 patients of the infectious group, 15 per cent, gave low readings, the figures being minus 14, minus 14, and minus 16. In none of the patients with low metabolic rates were there any of the classical symptoms of myxedema.

TABLE II

BASAL METABOLIC RATES CONT'D (SUMMARY OF TABLE I)

B.M.R. PER CENT	TOTAL NO. OF CASES	ALLERGIC ASTHMA	INFECTIOUS ASTHMA
+16 to +20	3	2	1
+11 to +15	1	1	0
+10	31	24	6
0			1
−10	22	14	8
−11 to −15	12	9	3
−16 to −20	2	1	1
−21 to −25	3	3	0
−28	1	1	0

TABLE III

RELATION OF BASAL METABOLISM TO ACTIVE SYMPTOMS

B.M.R. PER CENT	ALLERGIC ASTHMA		INFECTIOUS ASTHMA	
	ACTIVE	INACTIVE	ACTIVE	INACTIVE
+16 to +20	2	0	1	0
+11 to +15	0	1	0	0
+10	16	8	4	2
0			1	
−10	6	8	4	4
−11 to −15	6	4	0	2
−11 to −20	0	1	1	0
−21 to −25	1	2	0	0
−28	1	0	0	0

It seemed probable that the presence of active symptoms in a patient at or near the time of a metabolic rate reading could materially influence the result. We have therefore summarized in Table III the findings in the allergic and in the infectious groups on the basis of the presence or absence of active symptoms. The patients who had mild asthma at the time of the test, or who had had frank asthma within twelve hours preceding the test were designated as active. It will be noted that in both the allergic and infectious groups the patients with active symptoms tended to have higher readings. If, then, it had been possible to observe all our patients at a completely symptom-free time, the percentage of low readings found might have been even greater.

All patients were examined for the presence of thyroidal enlargement. We were surprised to find that 20 per cent of our patients had a definitely enlarged thyroid, and another 7 per cent were noted as having questionable thyroid enlargement. One third of the patients with enlarged thyroid also gave a family history of goiter. There are, unfortunately, no figures available on the incidence of goiter in this part of the country. This section of Pennsylvania is, however, not a goiter district and it is our impression, based on our experience in the medical wards of the University Hospital, that thyroidal enlargement would be found in less than 5 per cent of the population. On the other hand, the sex distribution of the thyroidal enlargement in this series is quite the same as that usually recorded in goiter districts—namely, about four females to one male. Twelve of the 15 goiters were noted in women, who comprised 33 of our 75 cases. In other words, one in every 4 female asthmatic patients had a goiter, while only one male

TABLE IV

THE INCIDENCE OF GOITER IN ASTHMATIC PATIENTS

	TOTAL CASES (75)		ALLERGIC ASTHMA		INFECTIOUS ASTHMA	
	M.(32)	F.(43)	M.(24)	F.(31)	M.(7)	F.(13)
Goiter	3	12	2	8	1	4
No Goiter	28	31	22	23	6	8
Family History of Goiter	1	5	1	5	0	0
Both Personal and Familial Goiter	1	4	1	4	0	0

asthmatic patient in 10 was so afflicted. It is perhaps significant that 11 per cent of the patients with allergic asthma gave a family history of goiter, while there was no such family history in the patients with infectious asthma.

Of the 15 patients with thyroid enlargement, the basal metabolic rate was normal (between plus 10 and minus 10) in 12 cases. One had a high reading (plus 20), two were low (minus 15 and minus 24).

We have been unable to reach any definite conclusion on the basis of these figures. That there is a lowered metabolic rate in bronchial asthma in an appreciable fraction of the cases would appear from our findings. Whether this lowered metabolic rate is due to lowered thyroid function or to altered function of other endocrine structures, as for example the adrenal, we do not know. The data on goiter would suggest thyroid hypofunction. If so, the question arises whether this hypofunction is to be interpreted in the nature of a cause or an effect. We are inclined to believe that in the majority of instances it is an effect. Certainly the feeding of thyroid extract has proved of no value in the great majority of cases. In one of our patients, however, both

the history and clinical findings were suggestive. A man aged thirty-five, with a positive family history of allergy and of goiter, developed classic exophthalmic goiter. Following a partial thyroidectomy which relieved his thyrotoxic symptoms he developed bronchial asthma. On several occasions thyroid feeding has given definite, but not permanent, relief from the asthma. Yet the patient's lowest metabolic rate as found by us was plus 1 per cent and after thyroid feeding rose to plus 10 per cent.

We noted in a number of asthmatic patients who were also afflicted with allergic eczema, that the metabolic rates seemed to be lower on the average than in the general asthmatic group. We therefore examined some patients with allergic eczema.

Our number of eczema cases is unfortunately too small to permit of any far-reaching conclusions. It is perhaps significant, however, that 7, or 41 per cent, of the 18 eczema cases, gave metabolic rate readings under minus 10, as opposed to 17, or 23 per cent, of the 75 asthmatic patients.

TABLE V

BASAL METABOLISM IN ALLERGIC ECZEMA

B.M.R. PER CENT	ECZEMA (18 CASES)	ASTHMA (75 CASES)
+11 to +20	2	4
+10	2	31
0		
−10	7	23
−11 to −20	5	13
−21 to −28	2	4

Here, again, we were unable to prove any etiologic relation between a possible hypothyroid function and the eczema present. Three eczema patients who were carefully observed while on thyroid therapy and whose metabolic rates were raised from minus 20 to plus 2; minus 18 to 0, and from minus 17 to plus 14, respectively, showed no resultant clinical improvement. This is all the more significant because only one (the third of these patients) showed any clinical evidence suggesting myxedema and this cleared up under thyroid therapy. It would seem probable that in these allergic eczema patients the low thyroid function is an effect and not a cause.

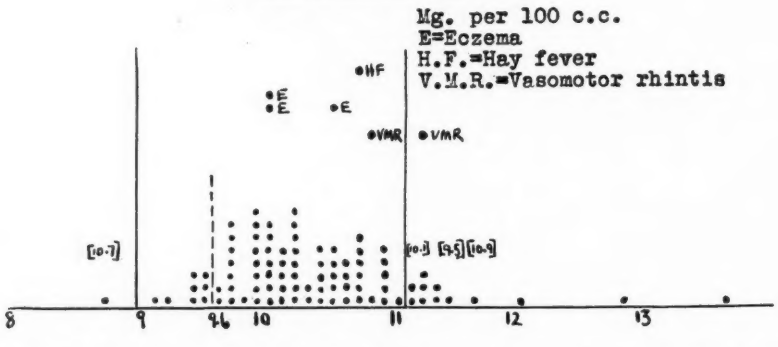
PART II. BLOOD CALCIUM STUDIES

Since Pottenger[9] in 1924 on the basis of three asthmatic patients treated with calcium intravenously (but in whom no blood calcium determinations were reported), suggested that a calcium deficiency may be present in bronchial asthma, there have been many and contradictory reports on this point. Brown and Hunter[10] in 1925, assuming 9.6 to 11 mg. per 100 c.c. as the normal range of blood calcium, reported figures in 166 cases of allergic disease, chiefly asthma, which

seemed to show a calcium deficiency in the majority of patients with allergic asthma. On the other hand, Criep and McElroy,[6] accepting 9 and 11.5 mg. per 100 c.c. as the normal limits of blood calcium, found the blood calcium to be within these limits in the great majority of the 80 asthmatic patients so studied. There is likewise a difference of opinion as to the state of the blood calcium in allergic persons. Greenberg and Gunther[11] in 1930 found the ratio between diffusible and nondiffusible calcium in asthmatic patients the same as that in normal individuals. On the other hand, Cantarow,[12] who made determinations of the total blood calcium and of the diffused calcium as found in the cerebrospinal fluid, found in allergic subjects a change in the ratio between the total and the diffused calcium. However, the number of cases studied is as yet too small to make the evidence conclusive.

CHART I

BLOOD CALCIUM

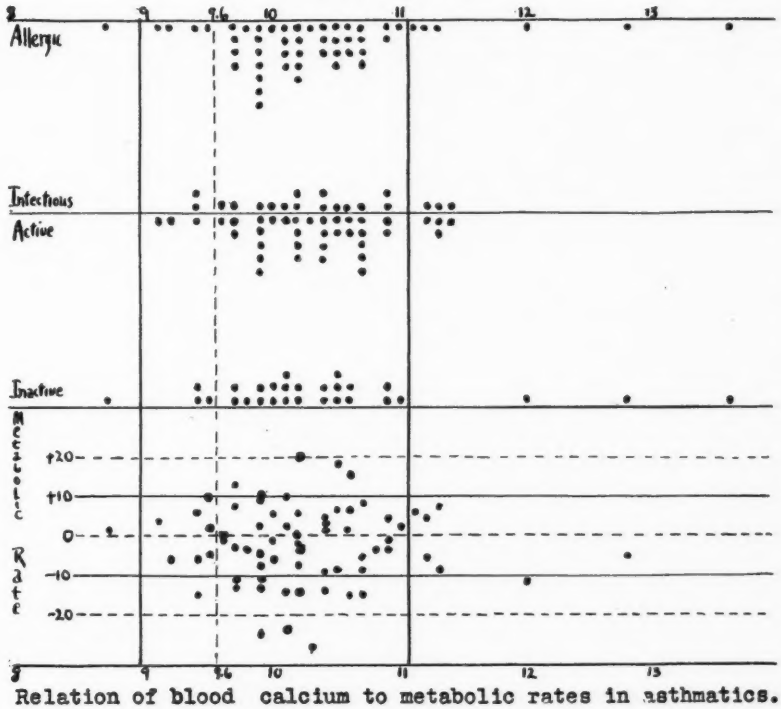


In Chart I are plotted 94 blood calcium estimations at the fasting level: 88 in asthmatic patients, three in allergic eczema patients, two in vasomotor rhinitis patients, and one in a hay fever patient. The technic was Clark and Collip's[13] modification of Kramer and Tisdall's method. Each dot represents one blood calcium estimation. If we accept 9 and 11 mg. per 100 c.c. as the lower and upper limits of normal, then nearly all of the estimations fall within the normal range. The only figure below 9 (8.7 mg.) was obtained in a patient who at the time had no asthma, but who on another examination and at a time when he did have asthma had a blood calcium of 10.7 mg. Likewise, of the 12 estimations over 11 mg., the two highest were in the same individual who was symptom-free, and in 3 other persons who were each found to have a normal blood calcium figure at another examination. The figures in brackets are the normal values obtained on another examination in 4 of the patients who also had given an abnormal reading. Brown and Hunter[10] suggested that blood calcium figures

below 9.6 must be considered abnormal. Even so, nearly all of our figures can still be considered normal and, if anything, on the high side of normal. Both of our vasomotor rhinitis patients gave high normal blood calcium figures, yet Novak and Hollander[14] claim the blood calcium is always below normal in this condition.

In the upper third of Chart II the blood calcium figures of the allergic and of the infectious asthmatic patients have been separately plotted. It will be seen that the incidence in both groups is about the same.

CHART II



Relation of blood calcium to metabolic rates in asthmatics.

Thinking that possibly the presence or absence of active asthmatic symptoms might be related to the blood calcium figure, we arranged the data on that basis in the middle section of Chart II. Here, again, there appears to be no relation between activity of symptoms and the blood calcium level.

In the lower third of Chart II are plotted the blood calcium figures of all those asthmatic patients in whom a basal metabolism study was made at about the same time that the blood calcium was determined. There seems to be no relation between the metabolic rate and the blood calcium level. The lowest basal metabolic figures, as well as a majority of the basal metabolic figures under minus 10, were found in

persons with normal blood calcium. All of the patients with elevated metabolic rates had normal blood calcium figures. Conversely, all the high and nearly all of the low blood calcium figures were obtained in patients with normal metabolic rates. Low metabolic figures were found both in patients with high and low blood calcium.

Kylin[15] has suggested that the calcium-potassium ratio is more important than the actual calcium level in the blood. We accordingly planned to make simultaneous estimations of total blood calcium and of blood potassium in our patients. The results were, however, so disappointing that after nine determinations in six patients we gave it up. The method used for the determination of potassium was that of Kramer and Tisdall[16] which proved rather difficult to manage in our hands. Under the best conditions it gave an error of 10 per cent.

TABLE VI

BLOOD CALCIUM: POTASSIUM RATIO IN ASTHMA

CASE	CALCIUM MG. PER 100 C.C.	POTASSIUM MG. PER 100 C.C.	CA:K RATIO	CONDITION AT TIME OF EXAMINATION
1	13.6	21.1	1.55	Marked asthma
	12.8	21.9	1.71	No asthma
2	10.7	20.0	1.87	Asthma
	8.7	21.0	2.41	No asthma
3	10.0	21.0	2.10	3 hours before paroxysm
	10.0	19.8	1.98	15 min. after onset of asthma
4	11.1	18.8	1.60	Marked asthma
5	10.8	23.0	2.12	Marked asthma
6	10.9	20.7	1.89	Moderate asthma

It will be seen from the few figures in Table VI that neither the potassium level nor the actual figure for the calcium-potassium ratio have any direct relation to the presence or absence of symptoms. Consequently, these figures have no absolute value in these cases. The only suggestive point is that in each of the 3 patients who were observed in an attack of asthma as well as in a symptom-free period, there was a fall in the ratio during the period of active symptoms. Yet even these changes might be accounted for wholly within the limits of error of the methods used.

As a result of these studies we are convinced that the determination of the total blood calcium is of no value in bronchial asthma. It is nevertheless possible that there may be an aberration from the normal in the total calcium metabolism. As in certain stages of parathyroid disorders there may be considerable alteration in the total calcium metabolism without material change in the blood calcium concentration, so, too, in determining the total blood calcium in bronchial asthma, we are measuring merely the depth of the stream and know nothing of the rate of flow. To our knowledge no studies in the total

calcium metabolism have been made in allergic persons. The same criticism applies, although probably in a lesser degree, to determinations of diffused and of nondiffusible calcium.

SUMMARY AND CONCLUSIONS

1. Patients with bronchial asthma frequently have a subnormal basal metabolic rate.

2. This tendency seems to be even more marked in patients with allergic eczema.

3. There is a higher incidence both of thyroid enlargement and of a family history of goiter in asthmatic patients than in the average population.

4. This would seem to suggest that the lowered metabolic rate is due to a depressed thyroid function.

5. Evidence is presented to show that in most instances the lowered thyroid function is probably an effect, not a cause of the allergic state.

6. Total blood calcium estimations in 75 patients with bronchial asthma were practically all within normal limits.

7. The blood calcium level bore no relation to the type of asthma (allergic or infectious), to the presence or absence of active symptoms, or to the basal metabolic rate.

8. The estimation of the total blood calcium percentage is of no value in bronchial asthma.

REFERENCES

1. Widal, F., and Abrami, P.: Effectual Action of Radiotherapy on Asthma in Hyperthyroidism, Presse méd. **32**: 473, 1924.
2. Kepinow, L.: The Thyroid Gland and Anaphylaxis: Influence of Thyroid on Anaphylactic Shock When Administered Orally a Short Time Before the Shock Injection, Compt. rend. Soc. de biol. **88**: 846, 1923.
3. Houssay, B. A., and Cisneros, A. D.: Anaphylactic Shock in Thyroprival Dogs, Rev. de la Soc. argent. de Biol. **1**: 156, 1925; also in Compt. rend. Soc. de biol. **93**: 886, 1925.
4. Nechkovitch, M.: Thyroid Gland in Anaphylaxis, Compt. rend. Soc. de biol. **91**: 809, 1924.
5. Popea, A., and Constantinescu, I.: Thyroid and Anaphylaxis, Compt. rend. Soc. de Biol. **90**: 720, 1924.
6. Criep, L. H., and McElroy, W. S.: Atopy; Blood Calcium and Gastric Analysis, Arch. Int. Med. **42**: 865, 1928.
7. Novak, F. J.: Basal Metabolism in Hyperesthetic Rhinitis, Wisconsin M. J. **19**: 534, 1921.
8. Simpson, W. L.: Basal Metabolism in Hyperesthetic Rhinitis and Bronchial Asthma, Laryngoscope **32**: 768, 1922.
9. Pottenger, F. M.: A Discussion of the Etiology of Asthma in Its Relationship to the Various Systems Composing the Pulmonary Neurocellular Mechanism With the Physiologic Basis for the Employment of Calcium in Its Treatment, Am. J. M. Sc. **167**: 203, 1924.
10. Brown, G. T., and Hunter, O. B.: Calcium Deficiency in Asthma, Hay Fever, and Allied Conditions, Ann. Clin. Med. **4**: 299, 1925.
11. Greenberg, D. M., and Gunther, L.: Diffusible Calcium of Blood Serum in Allergic Disease, Arch. Int. Med. **46**: 72, 1930.
12. Cantarow, A.: Diffusibility of Calcium in Bronchial Asthma, Am. J. M. Sc. **179**: 497, 1930.

13. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium With a Suggested Modification, J. Biol. Chem. **63**: 461, 1925.
14. Novak, F. J., and Hollander, A. R.: Influence of Ultraviolet Irradiation on Calcium Content of Blood Serum in Hay-Fever, Hyperesthetic Rhinitis and Asthma, J. A. M. A. **81**: 2003, 1923.
15. Kylin, E., and Myhrman, G.: Potassium and Calcium Content and Ratio in Serum in Physiologic Conditions; Adrenalin Reaction, Deutsch. Arch. f. klin. Med. **149**: 354, 1925.
16. Kramer, B., and Tisdall, F. F.: The Direct Quantitative Determination of Sodium, Potassium, Calcium, and Magnesium in Small Amounts of Blood, J. Biol. Chem. **48**: 223, 1921.

(For discussion, see page 507.)

HEAT SENSITIVENESS

Report of a Case*

R. A. Wilson, M.D.
Tucson, Arizona

CASES of physical allergy are rare enough in literature and in practice to report each one we may encounter. The following case presents an interesting phase which is suggested by Duke in his review of the physiology of heat production and heat loss.

H. T., a white male, 23 years of age, came to the Clinic on February 10, 1931, with a complaint of hives. For two years he had had an urticarial eruption on the skin every time he would get the least bit warm. This rash occurred first around the waist at his belt line; gradually, as it progressed, it spread over the entire trunk, abdomen, chest, back, and shoulders, not infrequently involving the upper extremities. It would begin with a flush of the skin and would soon develop into definite urticarial wheals and itching; these would soon subside upon cooling off but often tiny red papules persisted for several days over involved areas. The patient had recently come to Tucson from Iowa. In Iowa he always worked in shirt sleeves in winter to keep cool. He was able to do very little or no work in summer as a result of this urticaria. Since being in Tucson he had been unable to work because of the warm days, and he looked forward to a summer here with no little apprehension.

There was no history of any other allergy in the patient or his family.

Past History.—Irrelevant except a Neisserian urethritis several months before, a recurrence now with a slight discharge.

Physical Findings.—Temperature, 98°; pulse, 72; respiration, 18; blood pressure, 116/68. Patient was a well developed and well nourished white male adult who did not seem acutely ill. There were a few scattered reddish papules on chest, back, and arms. Teeth were in poor repair but there did not seem to be much, if any, periapical infection. Slight purulent discharge from urethra. Examination, otherwise, was entirely negative.

Laboratory Findings.—Uranalysis, negative except for many pus cells (urethritis). Hemoglobin, 100 per cent; R.B.C., 5,520,000; W.B.C., 9,000; differential, normal. Blood, Kahn and Kolmer tests, negative. Basal metabolic rate, minus 17 per cent. Urethral smear, positive for gonococcus.

*From the Section of Allergy, Thomas-Davis Clinic, Tucson, Arizona.

Patient was referred to the Genito-Urinary Department for treatment of urethritis. Desiccated thyroid gr. ⅓ three times daily was prescribed. Six days later he returned for check up; little, if any, improvement. Pulse, 84. He was advised to continue medication and report in another week. It was well over two months before I saw the patient again; but finally he came back to me for a certificate of health as a food handler. At this time I asked him how his urticaria was. He seemed surprised and replied that it was entirely well. He was working every day in a local dairy. He said he had had the prescription refilled four or five times (Thyroid gr. ⅓. Twenty-one tablets in each prescription filled.) that he would feel some tendency to recurrence and have it refilled; then take some and it would clear up. At this time the weather had become quite warm here.

COMMENT

The most pertinent question about this case is whether it is an allergic manifestation or not. When one is zealously looking for allergy in any and all of its ramifications, one is likely to classify certain symptoms and syndromes as allergic that another would place in a different field, so it is well to bring again to our attention the definition of allergy, of which there are many; the best of these being the simplest —a state of altered reactivity. "It is a broad term and under it can be described a group of peculiar phenomena of altered reactivity, the underlying cause of which is as yet unproved." (Quoted from Duke.) Hence a patient who reacts to physical agents such as heat, cold, light, etc., abnormally, is just as much allergic as those who have a paroxysm of sneezing when they inhale pollen to which they are sensitive.

Duke[1] has been the most eager proponent of this entity and has reported numerous cases. Henry[6] reported two cases—one of heat and effort sensitiveness, and one of both heat and cold sensitiveness. Brown and Horton[3] reported six cases of histamine-like reactions to cold. Alexander[4] reported one of heat sensitiveness. I feel that my case may justly be placed in this group.

There has been much discussion as to whether these so-called physical allergies are not really food sensitivities, histamine reactions, or even entirely outside the realm of allergy, as Piness[5] believes. It seems that this is a question that has been, and is, very difficult to prove, but it appears that there is sufficient evidence for us to conclude that they are not all due to food sensitivities. As to the histamine-like reactions, the cases observed by Brown and Horton would lead one to believe that a substance like histamine was liberated by the cold which gave rise to the reaction. Alexander's and Henry's cases were not due to reactions to foods, and they make no mention of histamine reactions. Alexander, however, states: "It appears that under various circumstances the skin of certain individuals has the capacity

of elaborating a histamine-like substance in excessive amounts. This induces localized swellings on the skin.''

My patient was not tested to foods, but his marked improvement on thyroid therapy leads me to doubt his being sensitive to foods.

Whether this case belongs to the field of endocrinology is problematical. It is not within the scope of this paper to discuss that phase of the subject; it is mentioned only as one of the important considerations of the subject in general.

I am aware that it is not proved by this report or by the reports of others that these cases belong in the field of allergy, but until more work is done to classify them properly and definitely, it seems they more nearly meet the requirements of allergy than any other category.

SUMMARY

1. A case is presented of a young male adult with hives brought on by any elevation of body temperature. He was found to have a lowered basal metabolic rate and was completely relieved by the administration of thyroid.

2. Some of the American literature of reports of similar cases is discussed in an effort to place these cases more definitely in the field of allergy.

REFERENCES

1. Duke, W. W.: Arch. Int. Med. **24**: 206, 1930.
2. Wells: Quoted from Duke, Asthma, Hay Fever, Urticaria and Allied Manifestation of Allergy, St. Louis, 1925, The C. V. Mosby Co.
3. Horton, B. T., and Brown, G. E.: Am. J. M. Sc. **178**: 191, 1929.
4. Alexander, H. L.: JOUR. ALLERGY **2**: 164, 1931.
5. Piness, G.: JOUR. ALLERGY **1**: 195, 1930.
6. Henry, J. P.: JOUR. ALLERGY **1**: 194, 1930.

Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

NINTH ANNUAL MEETING, PHILADELPHIA, PA., JUNE 8 AND 9, 1931

The Distribution of Reagins in the Blood Plasma. E. L. SHERRER, CLEVELAND, OHIO. (For original article, see page 467.)

DISCUSSION

DR. GEORGE PINESS, LOS ANGELES.—I want to ask one question and that is, how Dr. Sherrer brought down his various portions of albumin fraction by saturating with ammonium sulphate. That is what you used, is it not?

DR. SHERRER.—The globulins were separated into fractions; the albumins were not separated.

DR. PINESS.—Did you do each separately?

DR. SHERRER.—Yes.

DR. PINESS.—And you used ammonium sulphate free?

DR. SHERRER.—We take out one fraction of the protein and saturate to the next concentration and so forth.

DR. PINESS—How did you determine the euglobulin and globulin II?

DR. SHERRER.—The globulins are separated into the several fractions by variation in the salt concentrations. This is the standard method for protein fractionation.

DR. ISADORE PILOT, CHICAGO.—I think there is one point which Dr. Sherrer did not point out which may explain the point. He has a reagin reaction in all three fractions of his globulins because of the fact that it is practically impossible to get the pure fractions, euglobulin and pseudoglobulin I and II, and that may account for the fact that he got reactions in all three of these fractions.

It has been one of the difficulties in our chemistry to get absolute separation of these globulins.

DR. SHERRER.—In the paper I mentioned that I was not going to discuss the question whether these globulins are separate substances. Very great chemists, Sörenson, Howe and others are carrying out studies on these proteins. We took the method, which is the standard method for separating protein fractions, and the fraction which came down was considered as it is labeled in the slides. Whether each is an entity or not remains to be seen.

The Effect of Allergy on Allergen Absorption Following Parenteral Injections. MILTON B. COHEN, E. E. ECKER, AND J. A. RUDOLPH, CLEVELAND, OHIO. (For original article, see page 453.)

DISCUSSION

DR. MATTHEW WALZER, BROOKLYN.—I want to congratulate Dr. Cohen on a very nice piece of work. I am very glad to be able to say that I can confirm many of the findings of the speaker. I am not, however, ready to admit that the question of absorption in allergic individuals being diminished, is absolutely proved.

In my original paper on protein absorption, I showed that in atopic families parenteral absorption was diminished. I showed that this absorption was not due to any local factor in the intestinal tract or the stomach, but applied to the entire gastrointestinal tract and held for rectal absorption as well; in other words, we seem to be dealing here with a constitutional factor.

The fact that my strongest egg sample could not sensitize my fish-sensitive case, and my strongest fish serum could not sensitize my egg-sensitive case so that I could not demonstrate absorption in either of these cases, suggested to me that we were possibly not dealing with diminished absorption in atopic individuals but with diminished passive sensitization. This we have definitely demonstrated by titrating the ability to accept passive local sensitization in atopic individuals and titrating the same sample on normal individuals. We find a definite difference in the ability of atopics to accept passive local sensitization as compared to normals. However, I am not fully convinced that this is the entire explanation of the phenomenon and that there is not a diminished enteral and, as Dr. Cohen reports, respiratory absorption in atopic individuals.

DR. COHEN.—I should like to clarify the point which Dr. Walzer raised. In the work which we did in this series of patients, we determined that all accepted the transfer in reasonably high dilution of the antigen and that inability to accept transfer as suggested by Dr. Walzer could not explain our results. We feel that our experiments are conclusive enough in addition, to show that the delayed reactions are not the result merely of delayed absorption through the nasal mucous membrane but must be due to some parenteral factor, since when we inject the allergen subcutaneously or intramuscularly, we get delays similar to those following mucous membrane absorption. We are doing further work to attempt to clarify these issues.

The Effects of Fever Either Accidentally Incurred or Artificially Produced in Bronchial Asthma. SIMON S. LEOPOLD AND SLOAN G. STEWART, PHILADELPHIA, PA. (For original article, see page 425.)

Fever by Diathermy in the Treatment of Allergic Disease. SAMUEL M. FEINBERG, S. L. OSBORNE AND M. L. AFREMOW, CHICAGO, ILL. (For original article, see page 414.)

Hyperthermia Induced by High Frequency Electric Current in the Treatment of Intractable Asthma. HYMAN MILLER AND GEORGE PINESS, LOS ANGELES, CALIF. (For original article, see page 436.)

DISCUSSION

DR. JOSEPH L. MILLER, CHICAGO.—It seems to me from the paper that the effect of heat production by diathermy is not so efficient in bronchial asthma as is an acute infection. Bacterial infections of this type so frequently give the patient relief that we can almost predict that if a patient has a severe infection, he will be relieved of his asthma for a few weeks or longer. Of course, you cannot exactly simulate with this method of treatment the fever of an acute infection, but I wonder if there is not something else besides the heat that is responsible for the benefit we see in the acute infection.

DR. GEORGE L. WALDBOTT, DETROIT.—For some time I have been interested in investigating the influence of infectious disease on asthma by keeping very careful records of my patients in regard to this question. I have had a number

of patients who were decidedly relieved following an infectious disease, such as measles, pneumonia, etc. On the other hand I have seen patients who were made much worse by such a disease. There is no doubt in my mind that there must be some foreign protein substance which is formed in the system in consequence to a bacterial infection. This substance may under certain conditions temporarily desensitize a patient and under other conditions aggravate the allergic state in a manner similar to sensitization by the absorption of horse serum, pollen and other antigen.

Some time ago, I reported results similar to those the authors have just presented, obtained by means of irradiation of the spleen. Here also we probably encounter the liberation of a protein substance which is responsible for the therapeutic effect. The outcome of my investigation on x-ray treatment, although encouraging in certain instances, did not justify its routine application to every asthmatic.

DR. HARRY L. HUBER, CHICAGO.—I should like to ask one question. Have metabolic studies been made on these patients before treatment, during treatment, and after treatment?

DR. FRANCIS M. RACKEMANN, BOSTON.—I should like to remark that I have had some experience with injecting typhoid vaccine intravenously in doses of about 25 to 50 million. This treatment produces a fever for a few hours, and in most of the cases there is prompt relief from the symptoms. What the mechanism is and what the relation of this relief to the other relief obtained from fever alone is, I suppose it is quite impossible to say in our present knowledge, but I agree with Dr. Miller that there may be in typhoid vaccine and in the reaction produced by it, another factor that we do not know very much about.

DR. ISADORE PILOT, CHICAGO.—I should like to ask whether any studies were made on the nitrogenous constituents of the blood. In some work in the past with x-ray, in a very severe case I produced complete relief for at least one month. We found that the nonprotein nitrogen in one case rose from 25 to 45 milligrams, and cases exposed to milder doses did not get the marked improvement and did show the change in metabolism. We discontinued the use of x-ray because I think we endangered that patient with the severe reaction that was induced. That case suggested certainly that the improvement might be due to endogenous breaking down of proteins, causing manifest changes in blood chemistry.

DR. HARRY S. BERNTON, WASHINGTON.—We heard of the clinical improvement in the asthmatic by infection. I should like to call attention to the antithesis of this condition, namely, the terrible asthma that follows the acute infections. Certainly, in my experience with the war veterans, the worst possible type of case is the asthmatic who developed pneumonia and influenza in childhood. I cannot conceive of any worse condition than the asthma which follows whooping cough.

DR. MARION SULZBERGER, NEW YORK.—I was very much interested in these three papers, as all of us here must be, particularly because they show that we are beginning to recognize the fact that specific desensitization is by no means a panacea. A few years ago I think a great many of us would not have listened with so much interest to nonspecific measures for combating allergic conditions because we believed we had arrived at such excellent results by specific measures. I think we must continue to look for new nonspecific measures as well as continue to improve our methods of specific desensitization. One possible mechanism has not been mentioned today in regard to the effect of fever therapy; that is the purely functional effect on the autonomic nervous system. Some cases improve, and some cases instead of becoming better, become worse. We know exactly this from all the drugs which

affect the parasympathetic and the sympathetic nervous system. For instance, one case reacts well to ephedrine and another becomes worse.

I think further studies should be pursued. As a dermatologist I know I have been able to follow the effects of drugs upon skin lesions very accurately, and in some of them there is striking improvement from, for instance, pilocarpin. In others, the case becomes aggravated immediately from the same drug. We must recognize that all these fever therapies have in common a profound increase of perspiration and skin function, and there must be a tremendous influence upon the autonomic nervous system.

DR. W. W. DUKE, KANSAS CITY.—I have repeatedly observed that fever relieves asthma, even fever caused by infections such as pneumonia and in one case by a lung abscess. Either illness one would think should make asthma worse.

I am discussing this paper chiefly because of the fact that I think fever is the etiologic factor in a certain type of asthma, namely, the type caused by sensitiveness to heat or cold. Heat or cold sensitiveness can cause not only asthma but noninfectious coryza, urticaria, eczema and even gastrointestinal disturbances, bladder disorder and headache.

Heat and cold sensitiveness is caused primarily, I believe, by a disorder in the heat regulating mechanism.

In a matter of treatment I have used frequent alternations of heat and ice rubs with fair success in heat sensitive cases and with splendid results in cold sensitive cases.

DR. J. A. RUDOLPH, CLEVELAND.—We are all familiar with the fact that certain patients in all fields of medicine must be treated empirically. This is also true of many asthmatics in whom specific etiologic substances cannot be determined, and therefore nonspecific measures are resorted to. However, before resorting to nonspecific measures of therapy we must always remember that we are dealing with human beings and must, therefore, effect a thorough search of every possible clue for their difficulty before subjecting patients to unfamiliar methods. We must remember to be clinicians first and specialists later.

DR. LEON UNGER, CHICAGO.—I have been in touch with Dr. Feinberg on this diathermy work. The relief in some of these cases has been very good. You see some of the very severe, chronic asthmas, intractable asthmas, clear up. Even though it is only temporary (I believe the longest has had about three or four months of freedom), I think it is worth while to go on with work like that. If we can give temporary relief in some of the severe cases, the amount of work necessary is certainly worth while, and I do not think the work should be overthrown or discouraged by reports of lack of improvement in some cases.

I think Dr. Feinberg will go ahead with the work, and I hope he will be able to report again next year, with a much larger series of cases.

DR. JOSEPH L. MILLER, CHICAGO.—The fever which we get with the acute infections is a protein fever, probably largely due to protein derived from bacteria, partly protein from the damage to body cells. The fever we get with diathermy is apparently simply an overheat production which probably has nothing to do with protein. That might explain the difference in the results which you get by these two methods of treatment.

DR. MILTON B. COHEN, CLEVELAND.—I should like to add one point to clarify the discussion. I think that in order to draw conclusions it is essential that those working in this field differentiate between cases that show bronchopulmonary infection with asthmatic symptoms and those with true bronchial asthma. It is very difficult to do this clinically in every instance, at least in my experience, but I am certain that some cases which are considered bronchial asthma, at autopsy are found

to have none of the changes in the bronchial tree characteristic of asthma but show, instead, plugging of the bronchial lumen by purulent material. Unless all men working along these lines are talking about the same kind of patients, our conclusions will not be satisfactory.

DR. BALYEAT, OKLAHOMA CITY.—It is fairly generally accepted that the parasympathetic nerves have something to do with the spasm of the bronchial tree, and that the sympathetic nerves have something to do with the relaxation. If this be true, the patient who develops an infection of any part of the body, or who develops scarlet fever or lobar pneumonia or an acute appendicitis, theoretically ought to become free from asthmatic symptoms; as the same toxemia that stimulates the sympathetic nerves, thereby producing a lack of secretion in the mouth and intestinal tract, should in the same way stimulate the sympathetic nerves which oppose the parasympathetic nerves, thereby producing a relaxation of the bronchial tree. Clinically, patients who develop the diseases mentioned practically always become automatically free from asthma.

DR. LEOPOLD.—It seems quite obvious that it is fruitless to go ahead with this particular line of investigation. The unanimity of opinion that it is not productive of good results is fairly conclusive. I think it would be a good idea for those of us who are interested in fever therapy to try malarial treatment, provided we select proper cases. This form of therapy offers a much greater chance of success, because the mechanism of fever production in disease is probably entirely different than that produced by artificial means.

I am in accord with Dr. Rackemann's experience with intravenous typhoid vaccine except that I am afraid of it. I gave one patient with severe asthma an intravenous injection of typhoid vaccine and had the closest thing to a fatality that I ever saw which did not actually happen.

DR. FEINBERG.—The discussion has to do with the difference in effect of artificial fever, nonspecific therapy, and infection. How do we know it is not the same? How did Neymann? If he had assumed it was not the same, he would not have gone ahead and obtained the results with the diathermy fever in general paresis. I think we are assuming too much. We have to go ahead and try out our theories by experiment. We do not know the basis for either one, as a matter of fact.

As for aggravation of asthma due to infection, my experience has been that it is usually due to respiratory infection, and it is certainly gratifying to see that even some cases get better after respiratory infection, though most of the cases get worse with bronchitis and flu, and so forth.

I do not feel it is a panacea, but I differ with Dr. Leopold. I think it is worth while to go ahead with this series of cases judging by our results and the type of case we treated.

There were questions about nitrogen determination and metabolic studies. We have not done much on that. We have done the carbon dioxide combining power for acidosis. Some cases got more alkaline than acid, but most of them got more acid except when given alkalies.

As to the bronchitic type and allergic type, in our series there were several cases allergic, and apparently there was no difference. Some were benefited and some were not, and some of the other type were benefited and some were not.

DR. PINESS.—In answering Dr. Pilot I wish to stress the point that the theory on the treatment of paresis was based on the fact that heat destroys the spirochetes and was not dependent on any protein reaction, specific or nonspecific. At this time we should like to call your attention to the work of Shamberg along these lines on both animals and human beings. In the latter's work he used hot

baths, demonstrated definite destruction of the spirochetes and also demonstrated that there was no increase of nonprotein nitrogen in these cases. I do not agree with Dr. Pilot that heat is the important factor. However, I do feel, with Dr. Leopold, that it is worthless to carry on such experiments as these any further, because of the detrimental effect on the patient and the results not warranting further procedure along these lines.

Answering Dr. Cohen's discussion it seems to me that the essayists of the morning should be given credit for their ability to differentiate between asthma and other pulmonary conditions.

In reply to Dr. Waldbott, I am certain that were he to go back into the histories of many of his patients he would find that a greater number were relieved when suffering from acute infectious diseases than those made worse by the same condition.

The influenza type, or so-called asthmatic bronchitis, should not be classified in the group of straight bronchial asthma. These individuals develop immediately following or a short time after their influenza a characteristic train of symptoms which are persistent and eventually terminate in bronchospasm.

Studies in Urticaria: The Influence of Metabolic Factors. Leo H. Criep and Lawrence Wechsler, Pittsburgh, Pa. (For original article, see page 479.)

Basal Metabolism and Blood Calcium Studies in Asthma and Allergic Eczema. Richard A. Kern and Ida Teller, Philadelphia, Pa. (For original article, see page 488.)

The Basal Metabolic Rate in Allergic Disease. E. L. Alexander, Newport News, Va. (Abstract.)

Many instances are cited from the literature wherein various allergic conditions are associated with metabolic rates that are beyond the limits of normal. The abnormalities are not consistent in any direction, some being above and others below the normal basal rate. The cases reviewed include migraine in particular, but also cases of urticaria and angioneurotic edema, asthma and vasomotor rhinitis. In many of these cases therapy directed toward the thyroid gland resulted in considerable improvement.

The author discusses his series of 22 cases of allergy in which careful basal metabolism studies have been made. The average metabolic rate in this series is minus 17.5 per cent. Four case reports are given to exemplify the relationship between allergic symptoms and a low basal metabolism. In each instance thyroid therapy was instituted with marked improvement. The cases representative of allergy were asthma, migraine and urticaria with angioneurotic edema. Although striking results were obtained in the cases reported, the author states that not all of his cases responded to thyroid medication.

The Female Allergic Patient. Preliminary Report. HARRY L. HUBER, CHICAGO, ILL. (Abstract.)

This paper deals with a study of female patients who have allergy. It is pointed out that the symptoms of all allergic disorders are more severe during menstruation and pregnancy. Occasionally symptoms are lessened during pregnancy. It was noted that of the group of usual allergic manifestations, vasomotor rhinitis, urticaria, and angioneurotic edema occur in females much more frequently than in males. In a series of 200 patients with perennial vasomotor rhinitis it was noted that 80 per cent were female. In 60 per cent no extrinsic cause was found, and in 80 per cent there was no family history of allergy.

Detailed histories of these patients permit the prediction that in 75 per cent of women a rather typical history will be obtained. In early life there is no variation from the normal. In these women who have married there are no pregnancies, although they have wanted to have children, and they seem to be sterile. Nothing can be found to account for this sterility. The nasal symptoms are typical of those of vasomotor rhinitis and occur especially in the morning or when exposed to a sudden change in temperature. These patients are tired all the time. Physical examinations reveal nothing other than pale, boggy, nasal, mucous membranes. The blood pressure is usually below 110 mm. Laboratory findings show a tendency to a low basal metabolism but are otherwise negative. Treatment in these cases is without permanent relief.

An explanation is offered for the symptoms of these patients as follows: In man the nasal mucous membranes have a large venous supply forming a cavernous tissue over the lower turbinate, the lower and posterior portion of the middle turbinate, the posterior end and upper wall of the upper turbinate and the lower and posterior parts of the septum. In vicarious menstruation it is common to have nasal congestion and nose bleed. It is suggested that inasmuch as sex hormones may play some part in this disorder, they also may be responsible for nasal congestion in the type of woman described.

The paper also treats with the treatment of pregnant women who have pollinosis. It has been the experience of the author and others that in treating such patients, the usual doses of pollen extract may cause severe abdominal pain which is attributed to contraction of uterine smooth muscle. A suggested form of treatment consists of applying the proper pollens on the skin by means of scratch tests. These are applied at intervals of five to seven days. Sufficient pollen is applied to give an area of injection about the size of the palm of the hand. The site of application is changed at each visit. These patients are also instructed to avoid the pollen in so far as possible.

DISCUSSION

DR. JOSEPH L. MILLER, CHICAGO.—I am interested in basal metabolic studies. I am not certain whether Dr. Criep meant that this group had thyrotoxicosis or merely an increased basal rate.

I think the diagnosis of thyrotoxicosis is not a simple matter, and I suspect those with the higher rate had a thyrotoxicosis and the rate was due to that. We see many without palpable enlargement of the thyroid. They have an enlargement but it is posterior to the trachea. They have certain characteristics, however, which I believe enable you to say that this patient probably had a thyrotoxicosis, even if the basal rate may be plus 10 or less. There is the reaction of those people to excitement. The thyrotoxic patients react entirely differently from the normal. It is easy to distinguish that. While sitting quietly they may show a normal pulse, but with a little excitement the pulse goes up.

In this group where we have been in doubt as to whether the patient had a thyrotoxicosis, but where we were suspicious of it, we have given a small amount of iodin. We have used in all cases of thyrotoxicosis in preparing for operation 10 milligrams a day. If they respond very promptly with a falling basal rate, we say that patient had a thyrotoxicosis.

Then I think there is a great misuse of the term "hypothyroidism" confusing it with low basal rate. The only clinical picture we have of deficient thyroid is a myxedema. There may be a clinical picture which we cannot yet recognize which would enable us to say, "This is not, after all, a myxedema, but shows evidence of deficient thyroid," but at the present time we cannot, on a basal rate of minus 10 or minus 20, say this patient has hypothyroidism, for frequently when you bring the basal rate to normal the patient is no different; on the other hand, you can get a marked myxedema postoperative, with a minus 10.

I think we should refer to these as people with low basal rates and not as hypothyroidism.

DR. W. W. DUKE, KANSAS CITY.—In the study of patients with hay fever, asthma, or urticaria, I have done a great many basal metabolic tests and frequently found them 15 points above and below normal. The feature which impressed me most, however, was the instability of the rate, and the degree to which it could be affected by the application of heat or cold to the skin. I found only one case which had an enormous change in the metabolic rate. This was in a patient sensitive to cold. There were no signs of myxedema but the patient persistently ran a rate of minus 40 to minus 60. We raised the rate by causing him to have fever. The allergic symptoms all then immediately disappeared. He had no manifestations of hypothyroidism.

I have an interesting observation to report in relation to the female asthma patient. Several patients apparently were sensitive to their own breast milk. Each upon reduced withdrawal of milk had asthma or urticaria or both, and could be relieved by the use of a breast pump.

I had one patient who had not ceased secreting a little milk for a number of years after her last pregnancy. She could always squeeze as much as a teaspoonful of milk out of each breast. She had urticaria, dermatitis, and asthma. We could take her own milk and inject it in her skin and produce an enormous hive. I passively transferred her sensitiveness to several other people and produced huge reactions in the normal individuals upon injecting her milk into the passively sensitized areas. Cow's milk gave negative tests.

I did not have the opportunity of finding whether the reaction was caused by a decomposition product in her milk or by native proteins in her own milk. She was not sensitive to cow's milk.

DR. HARRY S. BERNTON, WASHINGTON.—This work has been most painstaking. I feel, however, that the above series of cases shows variations in blood determinations no different from a similar number of cases other than urticaria. The results are somewhat disappointing at least to me.

We all see patients with urticaria and are confronted with the difficulties of the condition. I have one patient who is subject to urticaria in a most virulent form. On one occasion she came to the office with a well-marked eruption of wheals and a large swelling of the hand.

I withdrew a small quantity of blood from a vein and injected 0.2 c.c. of whole blood intracutaneously in an area of the lower arm which was free of any eruption. Another specimen of blood was centrifugalized. The supernatant serum was similarly injected intracutaneously. Both tests were negative.

On another occasion specimens of stools and urine were collected during the height of an eruption of urticaria. The stools were first treated with ether and then subjected to the usual processes of protein extraction. The urine was evaporated to dryness and the residue extracted. In a series of cutaneous and intracutaneous tests with extract of stools and urine, the results were negative.

It has generally been accepted that the allergic state is a cellular and not an humoral affair. In the light of my observations, the conclusion seems warranted that in urticaria the reaction is that of irritable cells rather than that of irritating reagents within the blood stream.

A word or two about the use of calcium intravenously in the treatment of asthmatics. I am of the opinion that the blood calcium content bears no relation to the allergic state. I find that there is a certain percentage of patients who are distinctly helped by calcium therapy.

The case of asthma due to a mold, the *Aspergillus fumigatus*, which I reported in the *Journal of the American Medical Association*, July 19, 1930, was a victim of the disease for nine years. Every therapeutic procedure was tried to alleviate her distress, but without avail. Until the exact nature of the offending allergen was determined, the intravenous administration of calcium chloride was the only measure which afforded relief.

The soluble salts of calcium, administered intravenously, act as depressants to the central nervous system, and from that viewpoint their use in the treatment of asthma is justified.

Every year during the past several years, I have had at least two expectant mothers under preseasonal treatment for hay fever. The results have been most gratifying. In one patient a mild constitutional reaction occurred which had no effect on the course of the pregnancy. I find that pregnant women desire preventive treatments in order to be spared the agonies of hay fever.

DR. JOSEPH HARKAVY, NEW YORK CITY.—It is difficult, of course, to discuss all of the very interesting papers in this group, but there are several thoughts which arise in my mind to which I should like to give voice.

So far as urticaria is concerned, I think we must bear in mind in doing collateral studies, of the gastrointestinal tract, gall bladder, and so forth, not to lose sight of the fact that urticaria not only may be limited to the skin but may occur throughout the gastrointestinal tract. Such involvement may influence the functions of the affected organs and result in the abnormal figures which have been reported.

I remember a number of urticaria cases which gave defective gall bladder visualization and which on operation showed absolutely nothing in the gall bladder. As far as the various studies on basal metabolic rates are concerned and suggestions of the endocrine influence on asthma, you must remember that an allergic state may coexist in an individual who has various abnormalities related to his endocrine

system. Moreover, we must also bear in mind that the autonomic imbalance which admittedly exists in some individuals may influence the various glands of internal secretion and that which we consider as the cause may really be the end-result.

Thus, for example, we know that a woman who is disturbed about her menstrual period may get a suppression of menstruation. Psychic trauma may be a precursor to an attack of Basedow's disease. Facts such as these show the importance of the rôle of the mind and the autonomic nervous system and the proper function of the endocrine glands.

DR. MILTON B. COHEN, CLEVELAND.—I have a case similar to that of Dr. Huber's, a patient whose systemic reactions are invariably accompanied by uterine cramps; however, I think that is very rare and unusual. We treat our pregnant patients as if they were not pregnant and so far have had no difficulty.

I have been very much interested for a long time in calcium. If you test calcium on controlled patients, you find no clinical results. Recently I talked with a man who spent five years doing nothing but calcium determinations in a pediatric service where they study rickets. He can check calcium determinations within 10 per cent, that is a milligram in a hundred c.c. when you figure 10 as the normal, that means the normal may be up or down one; 9 to 11 for a man who is an expert. As done by the ordinary individual, there is probably 25 or 30 per cent error as far as total calcium is concerned.

Any of you who have ever dialyzed anything and then done chemistry on it know that when you begin tests there is an error of from 50 to 100 per cent, so when we read in the literature that so and so says he did so many cases and found such and such variations, unless they are very, very large, we had better take them with not a grain, but a teaspoonful, of salt before we apply them.

With regard to endocrine disturbances, it is my experience that the more scientific an endocrinologist is, the less he knows about endocrines. For instance, we have just heard that Dr. Rogoff, who has devoted his life to scientific endocrinology, would like to have an endocrine clinic. "I am not interested in goiters," he said, "and we know so little of other endocrine disturbances except Addison's disease that I fear my efforts would be useless."

I approve of all the bits of work being done to broaden our viewpoint with regard to these things, and this session has been a grand debunking session. I am glad to see this type of carefully controlled work done because I believe we, as a society, must stand for debunking a lot of ideas that are no good. If there is something in something, we want to know it, and I congratulate all these men here who have assisted in debunking some of these subjects.

DR. ALEXANDER STERLING, PHILADELPHIA.—With reference to the paper on calcium by Drs. Teller and Kern, several years ago I also found that the majority of allergic individuals had a normal or high normal blood calcium, and the impression gained by quite a few doctors, then, that there was a deficiency in calcium, was wrong. We have found a marked deficiency in phosphorus in allergic people.

It is not a metabolic question; it is a pharmacologic one. I agree with Dr. Bernton that quite a number of patients, whether giving a normal or high normal blood calcium, can be definitely improved by administration of calcium. It can be seen especially in a number of patients with hay fever who have a weeping mucous membrane that calcium taken orally produces better results. Some patients, properly desensitized for hay fever by the middle or the end of the season will still have a weeping mucous membrane, sneeze a little, and have a running nose. Yet, if given calcium the patient will feel better. That is similar to the administration of belladonna.

DR. ALBERT H. ROWE, OAKLAND.—I wonder if Dr. Criep would state how extensive his allergic studies were. I am anxious to know whether or not he went into the question of food allergy.

DR. H. CRIEP.—I want to thank Dr. Miller for his kindness in discussing my paper. The danger of covering a subject in a minimum amount of time is that one misses important points and in that way fails to drive home the point he is trying to make. I merely presented this series of patients as showing some changes in basal metabolic rate, without any reference to clinical hyper- or hypothyroidism, with the exception of one case where I indicated there was definite clinical evidence of hypothyroidism.

We realize how unreliable basal metabolic determinations are, and I presented them merely for what they are worth, indicating that they have no direct causal relationship to urticaria.

The idea I was trying to impress was not that functional disturbances in the gastrointestinal tract have a direct causal relationship to urticaria, but that they are present to some extent in these patients, and a functional disturbance in an allergic patient may mean something along the line of increased permeability of the gastrointestinal tract where in a normal person it may not produce any disturbance. These patients were studied from the allergic viewpoint with the food sensitization tests and also with trial diets.

These patients did get better using the treatment and the trial diets advised by Dr. Rowe.

Department of Reviews and Abstracts

Selected Abstracts

Treatment of Asthma by General Anesthesia. Troisier J., and Boquin, Y.: Bull. et mém. Soc. méd. d. hôp. de Paris **47**: 310, 1931.

The value of surgical intervention in certain cases of asthma is discussed. A case report is given of a patient aged thirty years, who had suffered from asthma from the age of three. The origin of the trouble appeared clearly to be alimentary. At the time at which the patient was seen, attacks were being precipitated without apparent cause, despite care as to diet, climate, therapeutic measures, etc. The thorax was emphysematous with a multitude of sibilant râles. Attacks of asthma occurred every night. Further examination revealed a tumor in the uterus. Preliminary injections of evatmine (0.5 mg. adrenalin and 1 c.c. extract of hypophysin) were given to ameliorate the asthma, and surgery was resorted to, which the patient underwent successfully.

Following the operation, the patient's asthma disappeared. No further attacks had occurred up to the time the patient was last seen —a period of seven months.

The authors, however, were unwilling to attribute the cure to the removal of the myoma. Their hypothesis is that in all probability the good effect was obtained by the general anesthesia. To test this theory, general anesthesia (without operation) was given to two other patients whose asthma had endured for a long period of time and resisted all the usual methods of treatment.

The patients, for several days preceding the anesthesia, were given injections of evatmine. An injection was also given the evening before and on the morning of the experimental anesthesia. Schleich's mixture was used because of its high ether content, and the patient was put to sleep under the mask of Ombredanne. Anesthesia was carried on from four to forty-five minutes.

The case reports are given. In both instances good results were obtained, although for a varying time period.

The analogy is pointed out between the successful use of ether anesthesia in the treatment of human beings and the successful prevention of anaphylactic shock in guinea pigs by the use of ether before

the otherwise shocking dose of protein is given. Treatment of patients by general anesthesia is not advocated except in certain cases where the asthmatic attacks have been stubborn and of long duration, failing to yield to the usual treatments.

The question is raised as to the probable duration of the therapeutic action of general anesthesia. No definite answer can be given, but it is believed that remissions (rather than actual cure) may be expected lasting sometimes for years, in refractory cases, perhaps only for weeks. The possibility is considered that the better results may be obtained when the previous injections of evatmine have ameliorated somewhat the asthmatic attack but have yet permitted the patient to go under the anesthesia while still struggling with his complaint.

Further research into the method is advocated by the authors. A discussion is appended.

Dermatitis Medicamentosa Due to Ephedrine. Ayres, S., and Anderson, N. P.: J. A. M. A. **97**: 437, 1931.

Two case reports are given in which dermatitis medicamentosa due to ephedrine was present. In both instances a nasal spray containing ephedrine had been used by the patient. Both a local dermatitis at the point of application and a more or less generalized eruption resulted. With the discontinuance of the nasal spray, prompt relief was experienced.

In Case I, there was a delayed positive skin reaction to a scratch test to ephedrine. The control area was defective. In Case II, a markedly positive reaction was obtained to a patch test. Attempts were made to demonstrate a passive transfer of sensitivity to ephedrine. The results were negative.

Procaine Dermatitis. James, B. M.: J. A. M. A. **97**: 440, 1931.

A case is reported in which the patient complained of swelling and inflammation of the upper and lower eyelids combined with a conjunctivitis of both eyes. The symptoms had been present for six months. She had been treated by several ophthalmologists with no results. It was decided to test the patient with pollens, the products of bacteria from the nasal secretion, and the cosmetics with which she came in contact. Patch tests were accordingly performed, which were negative except for the test to eye drops which the patient had been using over a considerable period of time. The prescription for the eye drops was obtained and found to contain procaine 1 per cent, boric acid and distilled water. Tests were then made with a 1 per cent solution of procaine in distilled water, and a positive result was elicited. The eye drops were discontinued, a bland ointment and x-ray treatment were substituted, and the symptoms of which the patient complained disappeared.

Further tests were made with various substances related to procaine and with the other local anesthetics, but no relationship could be determined between the constitutional formulas of the substances used and their irritant properties on the hypersensitive skin of the patient.

Hay Fever and Asthma Due to Red Cedar (Juniperus Virginiana) and to Mountain Cedar (Juniperus Sabinoides). Kahn, I. S., and Grothans, E. M.: Southern M. J. **24**: 729, 1931.

In the state of Texas, midwinter hay fever and asthma have been found often to be due to the pollen of mountain cedar, the pollination season extending from early December for about eight weeks. While in Florida, one of the authors noted a large number of cedars bearing a close resemblance to the cedars of Texas. Tests were made from the pollens of both cedars for a possible cross specificity. Patients sensitive to the mountain cedar were found to give positive reactions also to the red cedar. Patients sensitive to the pollen of the one, could be desensitized by injections of the pollen of the other.

It is noted that northern pollen cases often take on cedar sensitivity in Texas or in Florida.

The Use of Carbon Dioxide in the Treatment of Vasomotor Rhinitis, Hay Fever and Asthma. Hurst, A. F.: Proc. Roy. Soc. Med. **24**: 441, 1931.

The author, impressed with the benefits obtained in allergic conditions at Mont Dore, believes that these are due to the gases derived from the water there. These consist of over 99 per cent of carbon dioxide. To test this idea an apparatus was developed for giving carbon dioxide gas to patients with allergy. This consists of a small tank of the gas such as is used in an anesthesia apparatus. To the tank is attached a rubber tube, at the end of which is a nose piece. The nose piece is inserted in a glass of water and the gas released slowly until a moderately rapid stream of small bubbles is seen in the water. The nose piece is then dried and inserted into one nostril. The patient should breathe through his mouth and the gas be allowed to flow in the nose.

In cases of vasomotor rhinitis the treatment should be given from five to ten minutes each morning. In hay fever this should be done throughout the hay fever season, and the gas should be used as often as is necessary during the day and continued until the attack passes off.

For paroxysmal sneezing and nose-running the treatment should also begin immediately the attack begins. In cases of asthma which begin with sneezing the gas may prevent an attack from developing. The author does not know how the gas accomplishes these results, but believes the reaction is a direct one on the mucous membrane and is quite distinct from that produced by inhalation.

Bacteriologic Study on the Etiology of Bronchial Asthma. Storm Van Leeuwen, Anne J., and Maytum, C. K.: Proc. Staff Meetings Mayo Clinic **6**: 259, 1931.

The well-known fact that the first symptoms of asthma often occur after some acute respiratory infection indicates that infection may be causative in bronchial asthma. A study is presented of the bacteriology of asthma.

Freshly obtained sputum from selected patients was cultured on blood-agar plates and in tubes of glucose-brain broth. The cultures were incubated for from eighteen to twenty-four hours at 35° C. The primary cultures in glucose-brain broth were examined microscopically, plated on blood-agar and injected into guinea pigs. The cultures in glucose-brain broth yielded almost always a pure culture of green-producing streptococci. With these streptococci, guinea pigs were given intravenous and intratracheal injections in amounts of 0.5 c.c. of culture per 100 gram weight, at intervals of from two to fourteen days. Fifty guinea pigs were used. Symptoms resembling anaphylaxis appeared in five guinea pigs following the first injection. Five guinea pigs remained free from symptoms following from two to six injections. Eight died from other causes. The remaining 32 showed evidence of sensitization after repeated injections. In one guinea pig, severe, prolonged dyspnea was produced, resembling an acute asthmatic attack in a human. It lasted for twenty-four hours terminating in death with extreme emphysema of the lungs. All animals that died from symptoms of shock had pale, diffusely emphysematous lungs which floated high in water and had a greater volume than that found in normal guinea pigs.

The results, which not very striking, were considered interesting in that they resembled in many respects the results in humans following respiratory infections.

AUTHORS INDEX

A

ACQUARONE, PAUL, AND GAY, LESLIE N. A survey of the pollen flora in Baltimore during 1929, 336

AFREMOW, M. L. (*See* Feinberg, Osborne, and Afremow), 291, 414

ALEXANDER, E. L. The basal metabolic rate in allergic disease, 507

ALEXANDER, H. L. "Physical allergy." Report of a case with successful treatment, 164

— AND MCCONNELL, F. S. The variability of skin reactions in allergy, 23

B

BAIN, KATHERINE. (*See* Smyth and Bain), 177, 181, 282, 316

BECK, JAMES P. (*See* Fisher and Beck), 149

BECKER, F. E., AND BLACK, W. C. Investigations of the mechanism of the passive transfer of skin sensitization, 405

BELL, SAMUEL D. Transfer of skin-sensitizing antibodies, 398

BERG, SAMUEL. Relief of bronchial asthma following lobar pneumonia, 54

BLACK, J. H. A soluble specific carbohydrate of ragweed pollen, 161

BLACK, W. C. (*See* Becker and Black), 405

BRAY, GEORGE W. The hereditary factor in hypersensitiveness. Anaphylaxis and allergy, 205

BROWN, AARON, MILFORD, E. L., AND COCA, A. F. Studies in contact dermatitis. I. The nature and etiology of pollen dermatitis, 301

BULLEN, STEARNS S. The effect of tonsillectomy in allergic conditions, 310

BURKY, EARL. Staphylococcus filtrates, toxic and nontoxic; their use in intradermal studies, 387

C

CAULFEILD, A. H. W. Case report illustrating the nonspecific induction of local and general reactions in a hay fever (syphilitic) patient by the intravenous injection of neosol, 60

— AND LARUSH, F. Local passive transfer to a frequently recovered strain of staphylococcus hemolyticus. Case report, 372

CLARKE, J. A., JR. Presidential address: The Society for the Study of Asthma and Allied Conditions, The future of this society, 381

COCA, A. F. (*See* Brown, Milford, and Coca), 301

COHEN, MILTON B., AND RUDOLPH, J. A. A clinical study of the use of calcium in controlled cases of allergy, 34

—, ECKER, E. E., AND RUDOLPH, J. A. The effect of allergy on allergen absorption following parenteral injections, 453, 502

COLMES, ABRAHAM, MEDALIA, D., AND FACKTOROFF, E. The influence of adrenalin upon the vital capacity in asthma, 356

COOKE, ROBERT A. Some observations on infective asthma, 389

CRIEP, LEO H. The effect of bronchial asthma on the heart, 386

— AND WECHSLER, LAWRENCE. Studies in urticaria: The influence of metabolic factors, 479, 507

CROMWELL, HOBART W. (*See* Moore, Cromwell and Moore), 6, 85

D

DONNALLY, HARRY H. Vaccinial encephalomyelitis, 396

DUKE, W. W. The dropping out of pollen seasons. (Relation of the pollen content of the air to hay fever, asthma, and dermatitis of the exposed parts), 471

DURHAM, O. C. A comparison of ragweed pollen incidence in the United States for 1929 and 1930, 258

E

ECKER, E. E. (*See* Cohen, Ecker, and Rudolph), 453, 502

EFRON, B. G., AND PENFOUND, W. T. A nasal test with dry pollens in the diagnosis of seasonal hay fever, 43

ELLIS, RALPH V. A rational grouping of the food allergens, 246

EYERMANN, CHARLES H. Allergic headache, 106

F

FACKTOROFF, E. (*See* Colmes, Medalia, and Facktoroff), 356

FEINBERG, S. M., OSBORNE, S. L., AND AFREMOW, M. L. A new method of nonspecific treatment of allergic disease. Preliminary report, 291

—, —, AND —. Fever by diathermy in the treatment of allergic disease, 414, 503

FIGLEY, KARL D. The continuous method of hay fever treatment, 39

FISHER, A. MURRAY, AND BECK, JAMES P. Death in asthma. Report of a case without autopsy, 149

FORAN, FRANCIS L., AND LICHTENSTEIN, MEYER R. A study of the reaction in non-sensitive skin of mixtures in vitro of reagin and atopen, 291, 444

G

GAY, LESLIE N. Economic results from the treatment of pollen asthma and hay fever, 456

—. (*See* Acquarone and Gay), 336

H

HARKAVY, JOSEPH, AND MAISEL, FRED. Relationship of chronic sinus and pulmonary infections to bronchial asthma, 189

HAWKE, E. K. (*See* Vaughan and Hawke), 125

HOPKINS, J. GARDNER, WATERS, IRENE, AND KESTEN, BEATRICE. Elimination diets as an aid in the diagnosis and treatment of eczema, 239

HOPKINS, MARJORIE. Effect of weather variations upon the symptoms of hay fever patients, 145

HUBER, HARRY L. A critical analysis of the information obtained from hay fever sufferers, 48

—. The female allergic patient. Preliminary report, 508

K

KERN, RICHARD A., AND TELLER, IDA. Basal metabolism and blood calcium studies in asthma and allergic eczema, 488, 507

KERR, PHYLLIS S. (*See* Sulzberger and Kerr), 11

KESTEN, BEATRICE. (*See* Hopkins, Waters and Kesten), 239

L

LAMSON, R. W. (*See* Watry and Lamson), 272

LARUSH, F. (*See* Caulfeild and LaRush), 372

LEHRFELD, LOUIS. Vernal conjunctivitis, 328

LEOPOLD, SIMON S., AND STEWART, SLOAN G. The effects of fever, either accidentally incurred or artificially produced, in bronchial asthma, 425, 503

LICHTENSTEIN, MEYER R. (*See* Foran and Lichtenstein), 291, 444

M

MCCONNELL, F. S. (*See* Alexander and McConnell), 23

MCLAUGHLIN, JAMES. Blood Pressure in allergic individuals, 360

MAISEL, FRED. (*See* Harkavy and Maisel), 189

MARKIN, L. E. Report of 100 cases of local passive transfer of hypersensitiveness, 285

MEDALIA, D. (*See* Colmes, Medalia, and Facktoroff), 356

MILFORD, E. L. (*See* Brown, Milford and Coca), 301

MILLER, HYMAN. (*See* Piness and Miller), 73

— AND PINESS, GEORGE. Hyperthermia induced by high frequency electric current in the treatment of intractable asthma, 436, 503

MOORE, EDMOND E. (*See* Moore, Cromwell and Moore, 6, 85

—. (*See* Moore and Moore), 168

MOORE, MARJORIE B., AND MOORE, EDMOND E. Studies on pollen and pollen extracts. II. The absorption of allergically active constituents from pollen extracts, 168

—, CROMWELL, HOBART W., AND MOORE, EDMOND E. Studies on pollen and pollen extracts. IV. The allergically active constituent in pollen oil, 6

—, —, AND —. Studies on pollen and pollen extracts. V. Skin reactions to pollen fractions, 85

OSBORNE, S. L. (*See* Feinberg, Osborne, and Afremow), 291, 414, 503

P

PENFOUND, W. T. (*See* Efron and Penfound), 43

PINESS, GEORGE. (*See* Miller and Piness), 436, 503

— AND MILLER, HYMAN. The importance of food sensitization in allergic rhinitis, 73

R

RACKEMANN, FRANCIS M. Studies in asthma. X. Skin tests to foods in asthma, 113

— AND SMITH, LYMAN B. Studies in asthma: XII. The plant pollens of New England. Their relative importance, 364

RAPPAPORT, B. Z. A multiple scarifier for allergic tests, 379
RATNER, BRET. Dust hypersensitiveness with special reference to castor bean, 1
RICHET, CHARLES, JR. Food anaphylaxis, 76
ROWE, ALBERT H. Elimination diets for diagnosis and treatment of food allergy, 92
RUDOLPH, J. A. (*See* Cohen and Rudolph), 34
—. (*See* Cohen, Ecker and Rudolph), 453, 502

S

SHERRER, E. L. The distribution of reagins in the blood plasma, 467, 502
SMITH LYMAN B. (*See* Rackemann and Smith), 364
SMYTH, FRANCIS SCOTT. The toxic fraction of certain eczema serums, 173
— AND BAIN, KATHERINE. A study of the allergic skin test substance, 177
— AND —. Enteral absorption of the antigen and the apparent failure of antigen secretion in human milk, 282
— AND —. Studies in passive transfer, 181
— AND —. The direct skin test in allergy, 316
STEWART, SLOAN G. (*See* Leopold and Stewart), 425, 503
STRAUS, HENRY W. Artificial sensitization of infants to poison ivy, 137
STROUD, C. M. Allergic dermatitis, 118
SULZBERGER, MARION B., AND KERR, PHYLLIS S. Trichophytin hypersensitiveness of urticarial type, with circulating antibodies and passive transference, 11
SWERN, NATHAN. Incidence of diabetes mellitus in asthmatic patients, 375

T

TAUB, SAMUEL J., AND WHITE, CLEVELAND. Urticaria due to grass pollen, 186
TELLER, IDA. (*See* Kern and Teller), 488, 507

U

UNGER, LEON. The heart in bronchial asthma. An electrocardiographic study of 74 cases, 17

V

VAUGHAN, WARREN T., AND HAWKE, E. K. Angioneurotic edema with some unusual manifestations, 125

W

WATERS, IRENE. Elimination diets for the diagnosis and treatment of food allergy, 225
—. (*See* Hopkins, Waters and Kesten), 239
WATRY, ALVA, AND LAMSON, R. W. Botanic survey of Needles, California, with special reference to the hay fever producing flora, 272
WECHSLER, LAWRENCE. (*See* Criep and Wechsler), 479, 507
WESTON, CLIFFORD G. Studies in allergy. II. A case of sensitiveness to cuttlefish bone, 37
WHITE, CLEVELAND. (*See* Taub and White), 186
WILSON, R. A. Heat sensitiveness. Report of a case, 499

SUBJECT INDEX

A

Abstracts, 62, 130, 193, 293, 402, 513
Acid diet in treatment of bronchial asthma, 132 (Abst.)
Acid-base balance, allergy and, 133 (Abst.)
equilibrium in bronchial asthma, experiments on, 70 (Abst.)
Adrenalin, influence of, upon vital capacity in asthma, 356
Air, pollen content of, relation of, to hay fever, asthma, and dermatitis of the exposed parts, 471
Allegen absorption following parenteral injections, effect of allergy on, 453
horse, cat, and dog hair, identity of, 199 (Abst.)
Allergen-free room, basal metabolism determination in, 134 (Abst.)
Allergen-proof chambers, clinical treatment of asthmatic patients in, 404 (Abst.)
Allergens, food, 293 (Abst.)
rational grouping of, 246
Allergic dermatitis, 118
disease, basal metabolic rate in, 507
fever by diathermy in treatment of, 414
nonspecific treatment of, new method of, 291
eczema, basal metabolism in, 488
blood calcium studies in, 488
edema, 23
headache, 106
individuals, blood pressure in, 360
migraine, 63 (Abst.)
rhinitis, food sensitization in, importance of, 73
skin, desensitization of, mechanism of, 200 (Abst.)
skin-test substance, study of the, 177
tests, scarifier, multiple, for, 379
Allergically active constituent in pollen oil, 6
constituents, adsorption of, from pollen extracts, 168
Allergy, anaphylaxis and, 205
anatomic lesion of, the principal, 23
and acid-base balance, 133 (Abst.)
animal hair, identity of, 199 (Abst.)
calcium in controlled cases of, 34
controlled cases of, use of calcium in, 34
cuttlefish bone, sensitiveness to, case of, 37
direct skin test in, 316
Allergy—Cont'd
effect of, on allergen absorption following parenteral injections, 453
food, elimination diets for diagnosis and treatment of, 92, 225
histamine injections, 27
in ear, the middle and the internal, 402 (Abst.)
in urticaria factitia, indication of, 67 (Abst.)
nasal, as related to hay fever and hyperesthetic rhinitis, 135 (Abst.)
of the skin, theory of, 66 (Abst.)
physical, case of, with successful treatment, 164
relation of experimental rheumatoid inflammation to, 194 (Abst.)
skin reactions in, variability of, 23
test in, the direct, 316
studies in, 37
Anaphylactic and tuberculin type of hypersensitiveness, histologic study of skin reactions in, 201 (Abst.)
reactions to oxyuris, 64 (Abst.)
shock, fatal human, 62 (Abst.)
Anaphylactoid shock, 193 (Abst.)
Anaphylaxis and allergy, 205
calcium in, 194 (Abst.)
fatal, in man, 296 (Abst.)
food, 76
potassium in, 194 (Abst.)
Anesthesia, general, treatment of asthma by, 513 (Abst.)
Angioneurotic edema with some unusual manifestations, 125
Animal hair allergy, identity of, 199 (Abst.)
Antigen, enteral absorption of, and apparent failure of antigen secretion in human milk, 282
Apricot whip, recipe for, 236
Arsphenamine, hypersensitiveness of skin to, as determined by contact test, 70 (Abst.)
intradermal injection of, reactions of skin following, 297 (Abst.)
Association for the study of allergy, 502
Asthma, allergen-proof chambers in treatment of, 404 (Abst.)
anesthesia, general, treatment of, by, 513 (Abst.)
and hereditary syphilis, 134 (Abst.)
and syphilis, 134 (Abst.)
basal metabolism in, 488
blood calcium studies in, 488

Asthma—Cont'd
bronchial, acid diet in treatment of, 132 (Abst.)
acid-base equilibrium in, experiments on, 70 (Abst.)
bacteriologic study on etiology of, 516 (Abst.)
calcium in, diffusibility of, 68 (Abst.)
caused by liver and liver extract diet, 198 (Abst.)
effect of, on heart, 386
etiology of, bacteriologic study of, 516 (Abst.)
fever in, effects of, 425
following lobar pneumonia, relief of, 54
heart in, 17
physical method for treatment of, 403 (Abst.)
relationship of chronic sinus and pulmonary infections to, 189
carbon dioxide in treatment of, 515 (Abst.)
curve, influence of drugs on, 300 (Abst.)
death in, 149
sudden, 132 (Abst.)
diabetes mellitus in patients with, incidence of, 375
due to Juniperus Sabinoides, 515 (Abst.)
Juniperus Virginiana, 515 (Abst.)
mountain cedar, 515 (Abst.)
red cedar, 515 (Abst.)
hypochlorhydria of, in childhood, 294 (Abst.)
infantile, 65 (Abst.)
infective, some observations on, 389
intractable, high frequency electric current in treatment of, hyperthermia induced by, 436
hyperthermia produced by high frequency electric current in treatment of, 436
old-age, pathogenesis and therapy of, 197 (Abst.)
patients with, treatment of, in allergen-proof chambers, 404 (Abst.)
plant pollens of New England, their relative importance in, 364
pollen, economic results from treatment of, 456
research, 65 (Abst.)
skin tests to foods in, 113
studies in, 113, 364
sudden death in, 132 (Abst.)
therapy of, by respiratory treatment, 135 (Abst.)
true, treatment of so-called, 403 (Abst.)
vital capacity in, influence of adrenalin upon, 356
Asthma, vital—Cont'd
respiratory capacity in, diminution of, 298 (Abst.)
Asthmatic patients, clinical treatment of, in allergen-proof chambers, 404 (Abst.)
diabetes mellitus in, incidence of, 375
Atopic individuals, passive local sensitization in, 200 (Abst.)

B

Bacterial hypersensitivity of the intestinal tract, 196 (Abst.)
Bacteriologic study on etiology of bronchial asthma, 516 (Abst.)
Barley oatmeal muffin, recipe for, 237
Basal metabolic rate in allergic disease, 507
metabolism determination in allergen-free room, 134 (Abst.)
in allergic eczema, 488
in asthma, 488
Biscuits, homemade, recipe for, 236
Blood calcium in allergic eczema, 488
in asthma, 488
plasma, reagins in, distribution of, 467
pressure in allergic individuals, 360
Botanic survey of Needles, California, with special reference to hay fever producing flora, 272
Bronchial asthma, acid diet in treatment of, 132 (Abst.)
acid-base equilibrium in, experiments on, 70 (Abst.)
bacteriologic study on etiology of, 516 (Abst.)
calcium in, diffusibility of, 68 (Abst.)
caused by liver and liver extract diet, 198 (Abst.)
effect of, on heart, 386
etiology of, bacteriologic study on, 516 (Abst.)
fever in, effects of, 425
following lobar pneumonia, relief of, 54
heart in, 17
physical method for the treatment of, 403 (Abst.)
relationship of chronic sinus and pulmonary infections to, 189
Bronchitis, chronic, therapy of, by respiratory treatment, 135 (Abst.)
vital respiratory capacity in, diminution of, 298 (Abst.)
Brown sugar candy, recipe for, 235

C

Calcium, diffusibility of, in bronchial asthma, 68 (Abst.)
in anaphylaxis, 194 (Abst.)
in controlled cases of allergy, 34

Candy, brown sugar, recipe for, 235
chocolate, recipe for, 238
Carbohydrate, a soluble specific, of ragweed pollen, 161
Carbon dioxide in treatment of vasomotor rhinitis, hay fever and asthma, 515 (Abst.)
Castor bean dust hypersensitiveness, 1
Cedar, red and mountain, hay fever and asthma due to, 515 (Abst.)
Chicago Society of Allergy, 192, 291
Conjunctivitis, vernal, 328
Contact dermatitis, studies in, 301
test, hypersensitiveness of skin to arsphenamine as determined by, 70 (Abst.)
Corn crisps, recipe for, 234
pone, recipe for, 234
Correspondence, 204
Coryza, spasmodic, and conjunctival crises, 64 (Abst.)
Cuttlefish bone, sensitiveness to, case of, 37

D

Death in asthma, 149
Dermatitis, allergic, 118
contact, studies in, 301
medicamentosa due to ephedrine, 514 (Abst.)
pollen, nature and etiology of, 301
procaine, 514 (Abst.)
Desensitization of allergic skin, mechanism of, 200 (Abst.)
toward certain foods, oral method of, 130 (Abst.)
Diabetes mellitus, incidence of, in asthmatic patients, 375
Diathermy, fever by, in treatment of allergic disease, 414
Diet, acid, in treatment of bronchial asthma, 132 (Abst.)
elimination, as aid in diagnosis and treatment of eczema, 239
for diagnosis and treatment of food allergy, 92, 225
recipes for, 234
liver and liver extract, bronchial asthma caused by, 198 (Abst.)
restaurant, 232
Vanderbilt Clinic, 225
Drugs, influence of, on asthma curve, 300 (Abst.)
Dust hypersensitiveness, 1

E

Ear, middle and internal, allergy in, 402 (Abst.)
Eczema, allergic, basal metabolism in, 488
blood calcium in, 488
elimination diets as aid in diagnosis and treatment of, 239
in breast-fed infant, 282
serums, toxic fraction in certain, 173
Edema, allergic, 23
angioneurotic, with some unusual manifestations, 125
Electrocardiographic study of heart in bronchial asthma, 17
Elimination diets as aid in diagnosis and treatment of eczema, 239
for diagnosis and treatment of food allergy, 92, 225
recipes for, 234
Emphysema, therapy of, by respiratory treatment, 135 (Abst.)
vital respiratory capacity in, diminution of, 298 (Abst.)
Encephalomyelitis, vaccinial, 396
Epinephrin and ephedrin, chronic effect of, on nasal mucosa, 295 (Abst.)
Ephedrin, dermatitis medicamentosa, due to, 514 (Abst.)
Eye, sensitivity in treatment of, 297 (Abst.)

F

Fever by diathermy in treatment of allergic disease, 414
effects of, in bronchial asthma, 425
in bronchial asthma, effects of, 425
Flora, hay fever producing, botanic survey of Needles, California, with special reference to, 272
pollen, in Baltimore, survey of, during 1929, 336
Food allergens, 293 (Abst.)
rational grouping of, 246
allergy, elimination diets for diagnosis and treatment of, 92, 225
anaphylaxis, 76
desensitization toward certain, oral method of, 130 (Abst.)
sensitization in allergic rhinitis, importance of, 73
skin tests to, in asthma, 113
French dressing made with mineral oil, recipe for, 236

G

Gelatin, grape juice, recipe for, 238
grapefruit, recipe for, 235
lemon, recipe for, 237
plum, recipe for, 235
Grape juice gelatin, recipe for, 238
Grapefruit drink, recipe for, 235
gelatin, recipe for, 235
Grass pollen, urticaria due to, 186

H

Hay fever, carbon dioxide in treatment of, 515 (Abst.)
due to Juniperus Sabinoides, 515 (Abst.)
Juniperus Virginiana, 515 (Abst.)
mountain cedar, 515 (Abst.)
red cedar, 515 (Abst.)

Hay fever—Cont'd
effect of weather variations on, 145
local and general reactions, nonspecific induction of, by intravenous injection of neosol, 60
nasal allergy as related to, 135 (Abst.)
nonspecific induction of local and general reactions in, by intravenous injection of neosol, 60
pollen, economic results from treatment of, 456
producing flora, botanic survey of Needles, California, with special reference to, 272
seasonal, nasal test with dry pollens in diagnosis of, 43
sufferers, analysis of information obtained from, 48
treatment, continuous method, 39
weather variations, effect of, on, 145
Headache, allergic, 106
Heart, effect of bronchial asthma on, 386
in bronchial asthma, 17
Heat sensitiveness, 499
Hereditary factor in hypersensitiveness, 205
syphilis, asthma and, 134 (Abst.)
High frequency electric current in treatment of intractable asthma, hyperthermia induced by, 436
Histamine, 202 (Abst.)
injections, 27
shock, 193 (Abst.)
H-substance, 24
Hyperesthetic rhinitis, nasal allergy as related to, 135 (Abst.)
sodium iodide in, 296 (Abst.)
Hypersensitiveness, anaphylactic and tuberculin, histologic study of skin reactions in, 201 (Abst.)
castor bean dust, 1
dust, 1
first manifestation of the developing, 201 (Abst.)
local passive transfer of, report of 100 cases, 285
hereditary factor in, 205
of skin to arsphenamine as determined by contact test, 70 (Abst.)
to quinine, 63 (Abst.)
trichophytin, of urticarial type, 11
Hypersensitivity, bacterial, of the intestinal tract, 196 (Abst.)
Hyperthermia induced by high frequency electric current in treatment of intractable asthma, 436
Hypochlorhydria of asthma in childhood, 294 (Abst.)

I

Ice cream in elimination diets, 236
Indian pudding, recipe for, 235
Infantile asthma, 65 (Abst.)
Infective asthma, some observations on, 389
Intestinal tract, bacterial hypersensitivity of the, 196 (Abst.)
Intractable asthma, high frequency electric current in treatment of, hyperthermia induced by, 436

J

Juniperus Sabinoides, hay fever and asthma due to, 515 (Abst.)
Virginiana, hay fever and asthma due to, 515 (Abst.)

L

Lemon gelatin, recipe for, 237
ice, recipe for, 237
Lemonade, high caloric, recipe for, 237
Liver and liver extract diet, bronchial asthma caused by, 198 (Abst.)
Lobar pneumonia, relief of bronchial asthma following, 54
Local passive transfer of hypersensitiveness, report of 100 cases, 285
to a frequently recovered strain of staphylococcus hemolyticus, 372

M

Metabolic factors, influence of, in urticaria, 479
Metabolism, basal, in asthma and allergic eczema, 488
Migraine, allergic, 63 (Abst.)
Milk, human, enteral absorption of the antigen and the apparent failure of antigen secretion in, 282
Mineral oil, French dressing made with, recipe for, 236

N

Nasal allergy as related to hay fever and hyperesthetic rhinitis, 135 (Abst.)
mucosa, chronic effect of epinephrin and ephedrin on, 295 (Abst.)
test with dry pollens in diagnosis of seasonal hay fever, 43
Neosol, intravenous injection of, nonspecific induction of local and general reactions in hay fever by, 60
News item, 136
Nitrogen, distribution of, extracted by various solvents, 67 (Abst.)

Nonspecific induction of local and general reactions in hay fever by intravenous injection of neosol, 60

O

Oil, pollen, allergically active constituent in, 6
Old-age asthma, pathogenesis and therapy of, 197 (Abst.)
Oral method of desensitization toward certain foods, 130 (Abst.)
Oxyuris, anaphylactic reactions to, 64 (Abst.)

P

Pantopium hydrochloricum simulating protein sensitization, 63 (Abst.)
Pantopon, reaction to, simulating protein sensitization, 63 (Abst.)
Parenteral injections, allergen absorption following, effect of allergy on, 453
Passive local sensitization in atopic individuals, 200 (Abst.)
transfer, local, to frequently recovered strain of staphylococcus hemolyticus, 372
of hypersensitiveness, local, report of 100 cases, 285
of skin sensitization, mechanism of, 405
studies in, 181
trichophytin hypersensitiveness of urticarial type, with circulating antibodies and, 11
Physical allergy, case of, with successful treatment, 164
Plant pollens of New England, 364
Plasma, blood, reagins in the, distribution of, 467
Plum gelatin, recipe for, 235
Pneumotachographic studies, 300 (Abst.)
Poison ivy, artificial sensitization of infants to, 137
Pollen and pollen extracts, studies on, 67 (Abst.), 85, 168
asthma and hay fever, economic results from treatment of, 456
chemical studies on, 67 (Abst.)
content of air, relation of, to hay fever, asthma, and dermatitis of the exposed parts, 471
dermatitis, nature and etiology of, 301
dry, nasal test with, in diagnosis of seasonal hay fever, 43
extracts, adsorption of allergically active constituents from, 168
studies on, 6
flora in Baltimore, survey of, during 1929, 336
fractions, skin reactions to, 85
grass, urticaria due to, 186
Pollen—Cont'd
oil, allergically active constituent in, 6
plant, of New England, 364
ragweed, incidence in the United States, comparison of, for 1929 and 1930, 258
soluble specific carbohydrate of, 161
seasons, dropping out of, 471
studies on, 6, 85, 168
Potassium in anaphylaxis, 194 (Abst.)
Procaine dermatitis, 514 (Abst.)
Protein sensitization, reaction to pantopon simulating, 63 (Abst.)
skin test for, 23
Proteose in the urine, 130 (Abst.)
Pudding, Indian, recipe for, 235
poor man's rice, recipe for, 236
Pulmonary infections, relationship of, to bronchial asthma, 189
tuberculosis, calcium in, diffusibility of, 68 (Abst.)

Q

Quinine, hypersensitiveness to, 63 (Abst.)

R

Ragweed pollen incidence in United States, comparison of, for 1929 and 1930, 258
soluble specific carbohydrate of, 161
Reagin and atopen, mixtures of in vitro, reactions in non-sensitive skin of, 291, 444
Reagins in blood plasma, distribution of, 467
Recipes for elimination diets, 234
Respiratory capacity, vital, in chronic bronchitis, emphysema and asthma, diminution of, 298 (Abst.)
treatment of chronic bronchitis, emphysema and asthma, 135 (Abst.)
Rheumatoid inflammation, experimental, relation of, to allergy, 194 (Abst.)
Rhinitis, allergic, food sensitization in, importance of, 73
hyperesthetic, as related to hay fever, 135 (Abst.)
sodium iodide in, 296 (Abst.)
vasomotor, carbon dioxide in treatment of, 515 (Abst.)
Rye-rice muffins, recipe for, 236

S

Scarifier, multiple, for allergic tests, 379
Seasonal hay fever, nasal test with dry pollens in diagnosis of, 43
Sensitiveness, heat, 499
to cuttlefish bone, case of, 37
Sensitivity in treatment of the eye, 297 (Abst.)

Sensitization, artificial, of infants to poison ivy, 137
food, in allergic rhinitis, importance of, 73
passive local, in atopic individuals, 200 (Abst.)
protein, skin test for, 23
skin, passive transfer of, mechanism of, 405
Serums, eczema, toxic fraction in certain, 173
Shock, anaphylactic, fatal human, 62 (Abst.)
anaphylactoid, 193 (Abst.)
histamine, 193 (Abst.)
Sinus infections, chronic, relationship of, to bronchial asthma, 189
Skin, allergic, desensitization of the, mechanism of, 200 (Abst.)
allergy of the, theory of, 66 (Abst.)
hypersensitiveness of, to arsphenamine as determined by contact test, 70 (Abst.)
non-sensitive, reactions in, of mixtures in vitro of reagin and atopen, 291, 444
reactions of, following intradermal injection of arsphenamine, 297 (Abst.)
in allergy, variability of, 23
in anaphylactic and tuberculin type of hypersensitiveness, histologic study of, 201 (Abst.)
to pollen fractions, 85
sensitization, passive transfer of, mechanism of, 405
test for protein sensitization, 23
in allergy, the direct, 316
substance, allergic study of, 177
to foods in asthma, 113
transplants, tissue tubercle-allergy in, 66 (Abst.)
Skin-sensitizing antibodies, transfer of, 398
Sobee, recipes for, 238
Society for Study of Asthma and Allied Conditions, 189, 381
the future policy of, presidential address, 381
proceedings, 189, 291, 381, 502
Sodium iodide in hyperesthetic rhinitis, 296 (Abst.)
Spasmodic coryza and conjunctival crises, 64 (Abst.)
Staphylococcus filtrates, toxic and non-toxic, in intradermal studies, 387
hemolyticus, frequently recovered strain of, local passive transfer to, 372
Streptococci, apparent specificity among, 299 (Abst.)
Syphilis, asthma and, 134 (Abst.)
hereditary, asthma and, 134 (Abst.)

T

Tissue tubercle-allergy in skin transplants, 66 (Abst.)
Tonsillectomy, effect of, in allergic conditions, 310
Toxic fraction in certain eczema serums, 173
Transfer of skin-sensitizing antibodies, 398
Trichophytin hypersensitiveness of urticarial type, 11
Tuberculosis, pulmonary, calcium in, diffusibility of, 68 (Abst.)

U

Urine, a proteose in, 130 (Abst.)
Urticaria due to grass pollen, 186
factitia, allergy in, indication of, 67 (Abst.)
influence of metabolic factors in, 479
studies in, 479

V

Vaccines, mixed streptococcus, failure of, in treatment of chest colds and asthma, 299 (Abst.)
Vaccinial encephalomyelitis, 396
Vasomotor rhinitis, carbon dioxide in treatment of, 515 (Abst.)
Vernal conjunctivitis, 328
Vital capacity in asthma, influence of adrenalin upon, 356

W

Weather, effect of variations, upon hay fever, 145
Wheal of positive skin reaction, 23

The Journal of Allergy

H. L. ALEXANDER, M.D.,
Editor
600 S. Kingshighway
St. Louis, U. S. A.

WARREN T. VAUGHAN, M.D.,
Associate Editor
Medical Arts Bldg.
Richmond, U. S. A.

Published by THE C. V. MOSBY COMPANY, 3523-25 Pine Boulevard, St. Louis.

Published Bi-Monthly. Subscriptions may begin at any time.

Editorial Communications

Original Communications.—Manuscripts for publication, letters, and all other communications relating to the editorial management of the Journal should be sent to the Editor, H. L. Alexander, M.D., 600 South Kingshighway, St. Louis, Mo. Articles are accepted for publication upon the understanding that they are contributed solely to THE JOURNAL OF ALLERGY.

Neither the Editor nor the publisher accepts responsibility for the views and statements of authors as published in their "Original Communications."

Translations.—Manuscripts written in a foreign language, if found suitable for publication, will be translated without cost to the author.

Manuscripts.—Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. References should be placed at the end of the article and should include, in the order given, name of author, title of article, journal, volume, page, and year. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked on margin or back with the author's name.

Illustrations.—A reasonable number of half-tone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the editor for color plates, elaborate tables or extra illustrations. Copy for zinc cuts (such as pen drawings and charts) should be drawn and lettered only in India ink, or black typewriter ribbon (when the typewriter is used), as ordinary blue ink or colors will not reproduce. Only good photographic prints or drawings should be supplied for half-tone work.

Exchanges.—Contributions, letters, exchanges, reprints, and all other communications relating to the "Abstract Department" of the Journal should be sent to the Editor, H. L. Alexander, M.D., 600 South Kingshighway, St. Louis, Mo. Writers on subjects concerning allergy are requested to place this address on their regular mailing list for reprints.

Reprints.—Reprints of articles published among "Original Communications," must be ordered directly through the publishers. The C. V. Mosby Co., 3523-25 Pine Blvd., St. Louis, U. S. A., who will send their schedule of prices.

Review of Books.—Publishers and authors are informed that the space of the Journal is so fully occupied by matter pertaining to the branch to which it is devoted, that only works treating of this subject can be given attention. Send books to the Editor, H. L. Alexander, M.D., 600 South Kingshighway, St. Louis, Mo.

Business Communications

Business Communications.—All communications in regard to advertising, subscriptions, change of address, etc., should be addressed to the publishers, The C. V. Mosby Company, 3523-25 Pine Blvd., St. Louis, Mo.

Subscription Rates.—Single copies, $1.25. To anywhere in the United States, Cuba, Porto Rico, Canal Zone, Mexico, Hawaii and Philippine Islands, $7.50 per year in advance. To Canada and under foreign postage, $7.90.

Remittances.—Remittances for subscriptions should be made by check, draft, post-office or express money order, or registered letter, payable to the publishers, The C. V. Mosby Co.

Change of Address.—The publishers should be advised of change of subscriber's address about fifteen days before the date of issue, with both new and old addresses given.

Nonreceipt of Copies.—Complaints for nonreceipt of copies or requests for extra numbers must be received on or before the fifteenth of the month of publication; otherwise the supply is apt to be exhausted.

Advertisements.—Only articles of known scientific value will be given space. Forms close 15th of month preceding date of issue. Advertising rates and page sizes on application.

PROPHYLACTIC POLLEN EXTRACTS

in a New Package

GROUP 1. GRASSES (Bio. 360)
GROUP 2. CHENOPODS (Bio. 362)
GROUP 3. RAGWEEDS (Bio. 364)
GROUP 4. WORMWOODS (Bio. 366)

THERE are five or more different pollens in each group, but the atmospherically prevailing pollen predominates—in group 1, timothy; in group 2, Russian thistle; in group 3, the common and giant ragweed; and in group 4, mugwort.

Hitherto supplied in concentrated form, to be diluted for use, the grouped pollens are now available as glycerin extracts, so diluted as to contain in each cubic centimeter 20, 200, or 2000 pollen units, as labeled, each vial containing 4 c.c. So without any trouble at all the dosage can be begun at 2 units (0.1 c.c.) and run up to 1600 units, or even 2000 if the practitioner so elects.

The glycerin extracts retain their activity throughout the season, and every package is dated.

For Diagnosis. The same groups are supplied for diagnosis in glycerin-boric acid paste form, in small collapsible tubes, singly or in a package containing all four of the groups. *Single pollen extracts* in tubes can also be had.

Complete directions for use are given in the circulars accompanying the packages and in our booklet on Pollen Extracts in Hay Fever

PARKE, DAVIS & COMPANY

DETROIT, MICHIGAN

NEW YORK KANSAS CITY CHICAGO ST. LOUIS BALTIMORE NEW ORLEANS
MINNEAPOLIS SEATTLE
In Canada: WALKERVILLE MONTREAL WINNIPEG

THE RAGWEED SEASON IS FROM

AUGUST TO FROST

A BULLETIN—*2nd printing now available*

And it is important to emphasize that

COSEASONAL TREATMENT

i.e., treatment started after the onset of symptoms, is usually successful—and *quickly aborts the attack* as has been amply attested in the literature.

ARLCO-POLLEN EXTRACTS

provide the several ragweeds as regionally dispersed and are selected for delivery according to the locality.

If unavailable locally these extracts will be delivered direct postpaid, special delivery

LITERATURE AND REFERENCES ON REQUEST

THE ARLINGTON CHEMICAL COMPANY

YONKERS, NEW YORK